ONCOLOGIC DRUGS ADVISORY COMMITTEE BRIEFING DOCUMENT

Efaproxiral (RSR13) as an Adjunct to Whole Brain Radiation Therapy for the Treatment of Brain Metastases Originating from Breast Cancer

AVAILABLE FOR PUBLIC DISCLOSURE WITHOUT REDACTION

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LIST OF ABBREVIATIONS

2,3-DPG	2,3-diphosphoglycerate
µg	microgram
µm	micrometer
µM	micromolar
ASCO	american Society of Clinical Oncology
ASTRO	american Society for Therapeutic Radiology and Oncology
BCNU	carmustine, 1,3-bis (2-chloroethyl)-1-nitrosourea
BMD	brain metastases database
CI	confidence interval
cm	centimeter
C_{max}	maximum concentration
CNS	central nervous system
CO_2	carbon dioxide
CR	complete response
CT	computed tomography
CVAD	central venous access device
CYP2C9	hepatic microsomal cytochrome P450 enzyme
CYP3A4	hepatic microsomal cytochrome P450 enzyme
dL	deciliter
g	gram
GBM	glioblastoma multiforme
Gy	Gray
H^+	hydrogen
Hgb	hemoglobin
HR	hazard ratio
hr	hour
HW	high body weight
ICH	International Committee on Harmonization
IND	Investigational New Drug
IV	intravenous
kg	kilogram
KPS	Karnofsky Performance Status
L	liter
LW	low body weight
Max	maximum
mg	milligram
Min	minimum
min	minute
mL	milliliter
mM	millimolar
mm	millimeter
mmHg	millimeter of mercury
MMSE	Mini-mental State Examination
MRI	magnetic resonance image
MST	median survival time
n or N	number
n	Hill coefficient
N/A	not applicable
NABTT	New Approaches to Brain Tumor Therapy
NaCl	sodium chloride
NCI	National Cancer Institute
NDA	New Drug Application

NF	neurological Function
nm	nanometer
NSCLC	non-small cell lung cancer
OEC	oxygen equilibrium curve
p50	pressure of oxygen which results in 50% saturation of hemoglobin
PD	pharmacodynamic or progressive disease
PF	progression-free
pH	negative logarithm of the hydrogen ion concentration in the blood
PK	pharmacokinetic
pO_2	partial pressure of oxygen
PR	partial response
QOL	quality of life
RBC	red blood cell, erythrocyte
RPA	recursive partitioning analysis
RSR13	RSR13 Injection
RSR13AG	RSR13 acylglucuronide
RT	radiation therapy
RTOG	Radiation Therapy Oncology Group
SAP	statistical analysis plan
SD	standard deviation or stable disease
SO_2	oxygen saturation
SpO_2	arterial oxygen saturation measured by pulse oximetry
SRS	stereotactic radiosurgery
TRT	thoracic radiation therapy
WBRT	whole brain radiation therapy
WHOART	World Health Organization Adverse Reaction Thesaurus

1.0 INTRODUCTION

1.1 Indication

Registration is being sought for RSR13 (efaproxiral sodium) as an adjunct to whole brain radiation therapy (WBRT) for the treatment of brain metastases originating from breast cancer. Standard treatment for brain metastases consists of irradiation of the whole brain once a day, Monday through Friday, for 2 weeks. RSR13 is infused through a central venous access device (CVAD) at a dose of 75-100 mg/kg/day over 30 minutes with supplemental oxygen, with each of 10 fractions of WBRT administered within 30 minutes of end-infusion.

1.2 Current Therapy for Brain Metastases

It has been estimated that in the United States, between 80,000 and 170,000 individuals develop brain metastases each year, and up to 35,000 of these are patients with breast cancer.[1, 2] In addition, the incidence of brain metastases originating from breast cancer is rising due to the following: 1) longer survival resulting from earlier diagnosis, 2) better systemic therapy for extracranial disease, and 3) a higher detection rate due to improved neuroimaging techniques. Standard treatment for symptomatic lesions consists of corticosteroids and WBRT, which will relieve symptoms and temporarily improve neurological function in a majority of patients.[2, 3] In addition to WBRT and steroids (eg, dexamethasone), current management of patients with brain metastases includes anticonvulsant medication, surgical resection, stereotactic radiosurgery, and chemotherapy. WBRT is currently the principal nonsurgical means to achieve local control and has been shown to improve survival to approximately 4.5 months as well as improve/stabilize neurologic function. The current standard for WBRT is 30 Gy over 10 fractions (2 weeks).

Analysis of a large database compiled by the Radiation Therapy Oncology Group (RTOG) indicated that the overall prognosis for patients with brain metastases remains poor with a median survival time (MST) of 4.4 months (Table 1.1).[4] The results of this analysis showed that this patient population is heterogeneous with respect to prognostic factors and outcome. Despite the standard use of WBRT, the overall prognosis for patients with brain metastases has not changed over the last 25 years (Table 1.2).

Table 1.1
Recursive Partitioning Analyses (RPA) Radiation Therapy Oncology Group (RTOG)

Variable	Class I	Class II	Class III
KPS	≥70	≥70	<70
Primary Status	Controlled and <65 years of age and Brain only	Uncontrolled and/or ≥65 years of age and/or extracranial metastases	---
Age (years)			
Extracranial Disease			
%	20	65	15
Survival (months)	7.1	4.2	2.3

Source: Gaspar et al, 1997

Table 1.2
Results of Randomized Studies of WBRT for the Treatment of Brain Metastases

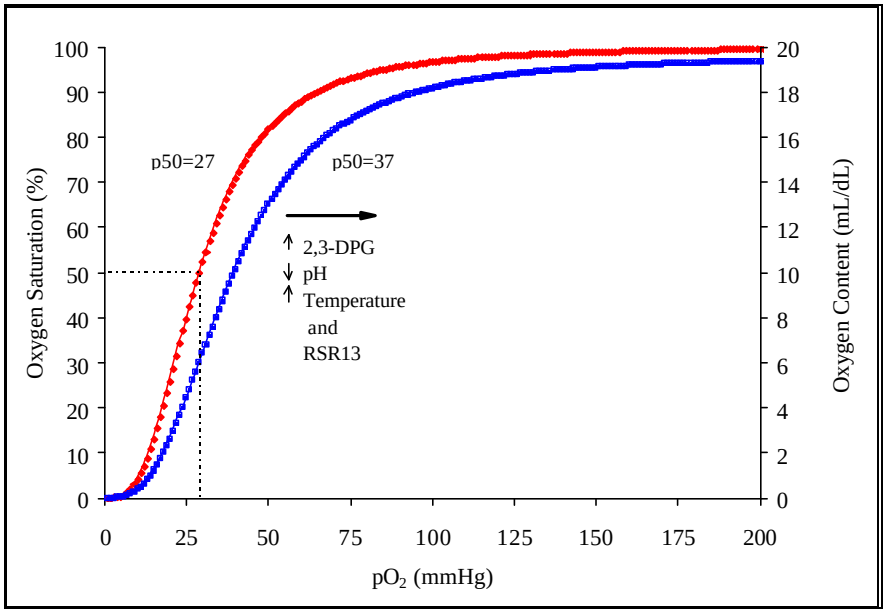
Study (Year Published)	N	WBRT Treatment Arms Total Gy/Number of Fractions	MST (months)
Harwood et al (1977)[5]	101	30/10 vs 10/1	4.0-4.3
Kurtz et al (1981)[6]	255	30/10 vs 50/20	3.9-4.2
Borgelt et al (1981)[7]	138	10/1 vs 30/10 vs 40/20	4.2-4.8
Borgelt et al (1981)[7]	64	12/2 vs 20/5	2.8-3.0
Chatani et al (1985)[8]	70	30/10 vs 50/20	3.0-4.0
Haie-Meder et al (1993)[9]	216	18/3 vs 36/6 vs 43/13	4.25.3
Murray et al (1997)[10]	445	54.4/34 vs 30/10	4.5

The efficacy of radiation therapy (RT) is affected by the extent of oxygenation in the tumor. Hypoxic tumors are more resistant to cell damage by radiation;[11] therefore, tumor hypoxia adversely affects the clinical prognosis of the patient receiving RT.[12-15] Oxygen measurements in human tumors have confirmed tumor hypoxia in glioblastoma multiforme (GBM),[16] brain metastases,[16, 17] squamous cell carcinomas of the uterine cervix[18] and head and neck,[19] and breast carcinoma.[20] Because hypoxic tumors are substantially more resistant to radiation than oxygenated tumors, even small hypoxic fractions in a tumor may limit the overall therapeutic effect of RT and increase the probability that some tumor cells will survive RT. Several clinical studies have demonstrated that tumors with a low median pO_2 (partial pressure of oxygen) have a higher in-field failure rate after RT. When compared to well oxygenated tumors of similar size and stage, patients with tumors of the uterine cervix have been found to have an increased recurrence rate if the median pO_2 is less than 10 mmHg.[18] This effect has also been demonstrated in head and neck cancer.[19]

1.3 Allosteric Modification of Hemoglobin

Hemoglobin is a tetrameric protein comprised of 2 pairs of symmetrically related a- and ß-globin chains. Each hemoglobin molecule is capable of binding 4 oxygen molecules. The percentage of oxygen-binding sites of hemoglobin bound with oxygen defines the fractional oxygen saturation and the oxygen content of the solution. The percent saturation is determined by the concentration of oxygen and the oxygen affinity of the binding site. Since oxygen is a gas, its concentration is described by the pO_2 (measured in mmHg) it produces in solution. The hemoglobin-oxygen saturation at any given pO_2 is graphically represented as an Oxygen Equilibrium Curve (OEC) (Figure 1.1). The pO_2 that results in 50% saturation of hemoglobin is identified as the p50. Thus, the p50 defines the position of the OEC. For example, a high p50 indicates a decreased affinity for oxygen and rightward shift of the OEC; a low p50 indicates an increased affinity for oxygen and a leftward shift of the OEC. An additional parameter in the description of the shift in OEC is the Hill coefficient (*n*), which is a numeric estimate of a change in the slope of the OEC. Both p50 and *n* are estimated by nonlinear regression using the following equation: $SO_2 = 100/(1 + (p50/pO_2)^n)$.

Figure 1.1
Oxygen Equilibrium Curve for Human Whole Blood



Allosteric modifiers of hemoglobin are molecules that alter the conformational structure of hemoglobin, and thus, modify the oxygen affinity of hemoglobin. Naturally occurring allosteric modifiers of hemoglobin include hydrogen ions (H^+), carbon dioxide (CO_2), and organic phosphates, the most important of which for human hemoglobin is 2,3-diphosphoglycerate (2,3-DPG). These natural molecules shift the OEC of hemoglobin to modulate oxygen availability in the tissues under various physiological conditions. Both acidosis and increased temperature cause a rightward shift of the OEC, resulting in an enhanced release of oxygen to the tissues. Acute altitude acclimation and anemia result in increased production of 2,3-DPG, again resulting in increased tissue oxygenation.

In the 1980s, 2 antilipidemic drugs were found to bind to hemoglobin resulting in a conformational change leading to a decrease of the affinity of hemoglobin for oxygen. The net effect was increasing the release of oxygen to tissues. In searching for a drug to treat sickle cell anemia, Abraham et al[21] discovered that the antilipidemic drug clofibric acid lowered the oxygen affinity of hemoglobin solutions. Later, Perutz et al[22] reported that another antilipidemic drug, bezafibrate, was much more effective. However, the potency of these antilipidemic drugs as allosteric modifiers of hemoglobin was inadequate for clinical use, due to dose-limiting toxicity at levels required to achieve a significant allosteric effect. Dr. Abraham's group subsequently designed and synthesized new allosteric modifiers using a structure-based drug design approach that combined the disciplines of x-ray crystallography, computer assisted drug design, and chemical synthesis. This research effort resulted in the identification of RSR13.

1.4 Mechanism of Action of RSR13

RSR13 is a synthetic allosteric modifier of hemoglobin, the first of this new class of pharmaceutical agents. RSR13 is a small molecule that binds noncovalently in the central water cavity of the hemoglobin tetramer and reduces hemoglobin oxygen-binding affinity. By facilitating the release of oxygen from hemoglobin, RSR13 causes an increase in whole blood p50 (pO_2 for 50% hemoglobin saturation), and an increase in tissue pO_2. RSR13 emulates the function of natural allosteric modifiers of hemoglobin (H^+, CO_2, and 2,3-DPG). The RSR13 therapeutic strategy of enhancing oxygen unloading from hemoglobin to tissue emulates and amplifies physiological tissue oxygenation. This approach has broad clinical applicability in indications characterized by tissue hypoxia including the use of RSR13 as an adjunct to RT. By reducing the oxygen-binding affinity of hemoglobin, RSR13 can enhance the oxygenation of hypoxic tumors. By this mechanism, RSR13 acts as a radiation sensitizer.

Nonclinical studies have shown that RSR13 is a potent allosteric modifier of hemoglobin and is capable of increasing the pO_2 of blood in vitro and in vivo. In vivo RSR13 increases tumor oxygenation and enhances the effectiveness of RT on hypoxic tumors. Data from pharmacology studies have demonstrated that RSR13 decreases hemoglobin oxygen-binding affinity, increases tumor oxygenation, and decreases the tumor hypoxic fraction. The studies also demonstrated that these effects of enhancing tumor oxygenation result in a selective augmentation of radiation toxicity to the hypoxic tumor while not affecting radiation toxicity to non-tumor tissue such as bone marrow or skin. In addition, studies have shown that RSR13 does not possess direct cytotoxicity.

The fact that RSR13 does not have to enter the cancer cells to increase the tumor sensitivity to RT is an essential differentiation from other pharmacologic attempts to improve the efficacy of cancer therapy. This is especially relevant in the setting of metastatic brain tumors, where the blood brain barrier acts to exclude or impede the entry of chemical agents into the brain parenchyma. Oxygen readily diffuses across the blood brain barrier and the cancer cell membrane to decrease tumor hypoxia and thereby increase the effectiveness of RT.

The goal of adjunctive RSR13 therapy is to achieve maximal concentrations of oxygen in the tumor during administration of WBRT in order to decrease the hypoxic fraction of tumors and increase the tumor sensitivity to WBRT. The maximum pharmacodynamic effect of RSR13 occurs at the end of RSR13 infusion; therefore, the timing of administration for the WBRT fraction should be within 30 minutes of RSR13 administration. To optimize tumor oxygen delivery and ensure sufficient arterial oxygenation during the period when oxygen affinity is reduced by RSR13, patients receive supplemental oxygen via nasal cannula. Supplemental oxygen is initiated prior to RSR13 infusion, administered continuously during each RSR13 infusion, and continued during WBRT until a protocol defined time-point.

2.0 BACKGROUND

2.1 Clinical Development of RSR13

RSR13 has been studied for the treatment of cancer patients in 15 Phase 1 to Phase 3 clinical studies under oncology Investigational New Drug (IND) 48,171. RSR13 has been studied in patients with GBM, brain metastases, and locally advanced, unresectable non-small cell lung cancer (NSCLC) (Table 2.1).

Table 2.1
Completed and Ongoing RSR13 Oncology Studies

Study Number	N	Study Title	RSR13 dose (mg/kg)	Status
RT-002	20	A Phase 1b Study to Evaluate the Safety and Tolerance of Multiple Daily Intravenous Doses of RSR13 Administered to Patients Receiving Concurrent Radiation Therapy	75, 100	Complete; Reported
RT-004	12	A Phase 2 Study to Evaluate the Effects of a Single Intravenous Infusion of RSR13 on Tumor Oxygenation in Patients with Tumors Amenable to Oxygen Determination Measurements	*RSR13*: 100 *Placebo:* 0.45% NaCl	Complete; Reported
RT-006	19	A Phase 1b Study to Evaluate the Safety and Tolerance of Repetitive Daily Intravenous Doses of RSR13 Administered to Patients Receiving Cranial Radiation Therapy for Glioblastoma Multiforme	100	Complete; Reported
RT-007	50	A Phase 2 Study to Evaluate the Efficacy and Safety of Repetitive Daily Intravenous Doses of RSR13 Administered to Patients Receiving Cranial Radiation Therapy for Glioblastoma Multiforme	100	Complete; Reported
RT-007b	67	A Companion Phase 2 Study to Evaluate the Efficacy and Safety of Repetitive Daily Intravenous Doses of RSR13 Administered to Patients Receiving Cranial Radiation Therapy for Glioblastoma Multiforme	100	Complete; Reported
RT-008	69	A Phase 2 Study to Evaluate the Efficacy and Safety of RSR13 Administered to Patients Receiving Standard Cranial Radiation Therapy for Brain Metastases	100 with dose reductions to 75 or 50 allowed	Complete; Reported
RT-009	538	A Phase 3 Randomized, Open-Label, Comparative Study of Standard Whole Brain Radiation Therapy, With or Without RSR13, in Patients with Brain Metastases	*RSR13:* 100 with dose reduction to 75 allowed *Control*: No RSR13/ no placebo	Complete; Reported
RT-010	51	A Phase 2 Study of Induction Chemotherapy with Paclitaxel and Carboplatin Followed by Radiation Therapy with RSR13 for Locally Advanced Inoperable Non-Small Cell Lung Cancer	75 with dose adjustment to 50 or 100 allowed	Complete; Reported
RT-012	70[a]	A Phase 1/2 Study to Evaluate the Safety, Tolerance, and Efficacy of RSR13 (Efaproxiral) Administered to Patients Receiving a Course of Cisplatin and Radiation Therapy for Locally Advanced Carcinoma of the Cervix	25-100 to determine maximum tolerated dose	Study Ongoing
CT-001	70[a]	A Phase 1/2 Study to Evaluate the Safety and Tolerance of Escalating Doses of RSR13 (Efaproxiral) Administered with a Fixed Dose of BCNU Every 6 Weeks in Patients with Recurrent Malignant Glioma	25-100 to determine maximum tolerated dose	Study Ongoing

Study Number	N	Study Title	RSR13 dose (mg/kg)	Status
RT-014	22[a]	A Phase 1 Open-label Study of RSR13 (efaproxiral) and Supplemental Oxygen with Concurrent Paclitaxel, Carboplatin, and Thoracic Radiation Therapy in Patients with Locally Advanced, Unresectable (Stage IIIA/IIIB) Non-small Cell Lung Cancer	50-75 to determine maximum tolerated dose	Study Ongoing
RT-016	360 [a]	A Phase 3 Randomized, Open-Label Comparative Study of Standard Whole Brain Radiation Therapy with Supplemental Oxygen, with or without Concurrent RSR13 (efaproxiral), in Women with Brain Metastases from Breast Cancer	*RSR13:* 100 with dose reduction to 75 allowed *Control*: No RSR13/ no placebo	Study Ongoing

N: total number of patients enrolled
[a]Number of patients planned

Two studies were designed to provide efficacy data for the use of RSR13 as an adjunct to WBRT plus supplemental oxygen in the treatment of patients with brain metastases: the Phase 2 study, RSR13 RT-008,[23] and the Phase 3 study, RSR13 RT-009. The main goal of concurrent administration of RSR13 and WBRT plus supplemental oxygen in the treatment of brain metastases was to show improvements in survival and response rate. The Phase 2 (RT-008) survival analyses were prospectively designed per protocol to be compared to the survival results of the RTOG Brain Metastases Database (BMD). Findings indicated that RSR13 improves the efficacy of WBRT plus supplemental oxygen in patients with brain metastases.

In view of the encouraging results of RT-008 and the high unmet medical need for effective treatment in patients with brain metastases, the Phase 3 study (RT-009) was designed to test the hypothesis that the addition of RSR13 to WBRT plus supplemental oxygen would improve survival and response rate when compared to WBRT plus supplemental oxygen alone. Patients receiving daily intravenous (IV) doses of RSR13 with supplemental oxygenadministered immediately prior to standard WBRT were compared to patients receiving daily standard WBRT with supplemental oxygen (without a placebo). The patient groups analyzed in this study included the predefined co-primary populations of all eligible patients and eligible patients with NSCLC/breast cancer primary. Additional analyses by stratum and by primary tumor type were performed (NSCLC, breast, and other primary tumor types). In both co-primary populations, RT-009 showed a decreased risk of death associated with RSR13 compared to the control when analyzed by Cox multiple regression model. In addition, with additional follow-up, an improvement in survival was observed in eligible NSCLC/breast primary patients. It was apparent, however, that these results were in large part driven by the treatment effect observed in patients with breast cancer. In these patients, a significant difference in survival (using log-rank and Cox multiple regression model) favoring RSR13 as an adjunct to WBRT plus supplemental oxygen (MST, 8.7 months) versus WBRT plus supplemental oxygen alone (MST, 4.6 months) was observed. These results were supported by the response rate improvement in RT-009 as well as evidence from RT-008 in the same patient population. Based on these results, Allos Therapeutics, Inc. submitted the New Drug Application (NDA) for RSR13 as an adjunct to WBRT for brain metastases in patients with breast cancer.

2.2 Clinical Pharmacology and Metabolism

2.2.1 Clinical Pharmacology Studies

The clinical pharmacology results in this section were based on studies with RSR13 doses of 10-100 mg/kg, administered by constant-rate, IV infusions over 30-60 minutes, with RT administered within 30 minutes of end-infusion. The descriptions of dosing for the 9 clinical studies are summarized in Table 2.2.

Table 2.2
RSR13 Studies That Have Provided PK and/or PD Data for the Oncology Indication

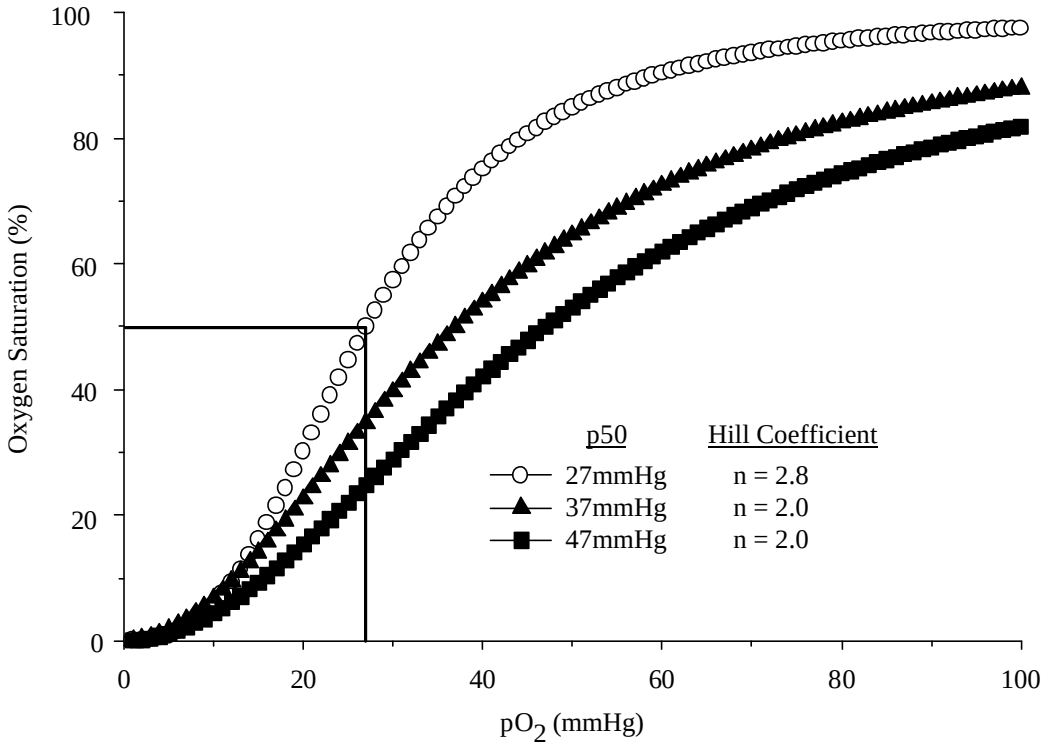
Study Number	Description of Dosing
HV-001	A single dose, dose-escalation study (10-100 mg/kg) in healthy young male and female patients
HV-003	A single dose study to evaluate the mass balance of a single 75 mg/kg IV dose of RSR13 to healthy male and female patients`
RT-002	A multiple dose, dose- and schedule-escalation study in cancer patients receiving palliative RT, utilizing doses of 75-100 mg/kg for up to 5 days per week for 2 weeks, 10 total doses.
RT-004	A single RSR13 dose study to evaluate the effect of a single 100 mg/kg IV dose of RSR13 on tumor oxygenation.
RT-006	A repetitive dose, schedule-escalation study in patients receiving a 6-week course of cranial RT for GBM, utilizing 100 mg/kg dose every other day versus every day for a total of either 15 or 30 doses
RT-007	A repetitive dose study in patients receiving a 6-week course of cranial RT for GBM, utilizing RSR13 100 mg/kg dose for a total of 30 doses
RT-008	A repetitive dose study in patients receiving a 2-week course of cranial RT for brain metastases secondary to breast, NSCLC, melanoma, genitourinary or gastrointestinal primary cancer, utilizing RSR13 75-100 mg/kg dose (with dose modifications to 50 mg/kg or omission) for a total of 10 doses
RT-009	A repetitive dose study in patients receiving a 2-week course of cranial RT for brain metastases secondary to breast, NSCLC, melanoma, genitourinary or gastrointestinal primary cancer, utilizing 75-100 mg/kg dose (with dose modifications to 50 mg/kg or omission) for a total of 10 doses
RT-010	A repetitive dose study in patients undergoing a 6-7 week course TRT for NSCLC (subsequent to 2 cycles paclitaxel and carboplatin 3 weeks apart) utilizing RSR13 75 mg/kg with dose adjustments to 50 or 100 mg/kg

2.2.2 Results from Pharmacokinetic/Pharmacodynamic Studies and RSR13 Dose Selection

The goal in dosing RSR13 is to shift the hemoglobin-oxygen dissociation in order to maximize the potential oxygen concentration gradient to facilitate diffusion of oxygen into the tumor; therefore, the greater the shift in p50 the greater the oxygen dissociation. However, RSR13 also affects the *n* (Hill coefficient). This combination of effects is illustrated in Figure 2.1. The progressive increase in p50 and decrease in *n* causes the curve on the left to flatten forming the curve on the right. The impact of the flattening is that it becomes more difficult to saturate hemoglobin with oxygen in the pulmonary circulation, even with supplemental oxygen. Therefore, based on the competing effects on hemoglobin-oxygen-binding affinity, it was determined that a target shift in p50 of 10 mmHg provided for oxygen dissociation, while still

allowing sufficient cooperativity to assure sizable saturation in the pulmonary circulation, in order to provide the greatest oxygen gradient to enhance tumor oxygenation and radiation sensitization.

Figure 2.1
Oxygen Equilibrium Curve for Human Whole Blood and the Relationship of p50 and the Hill Coefficient

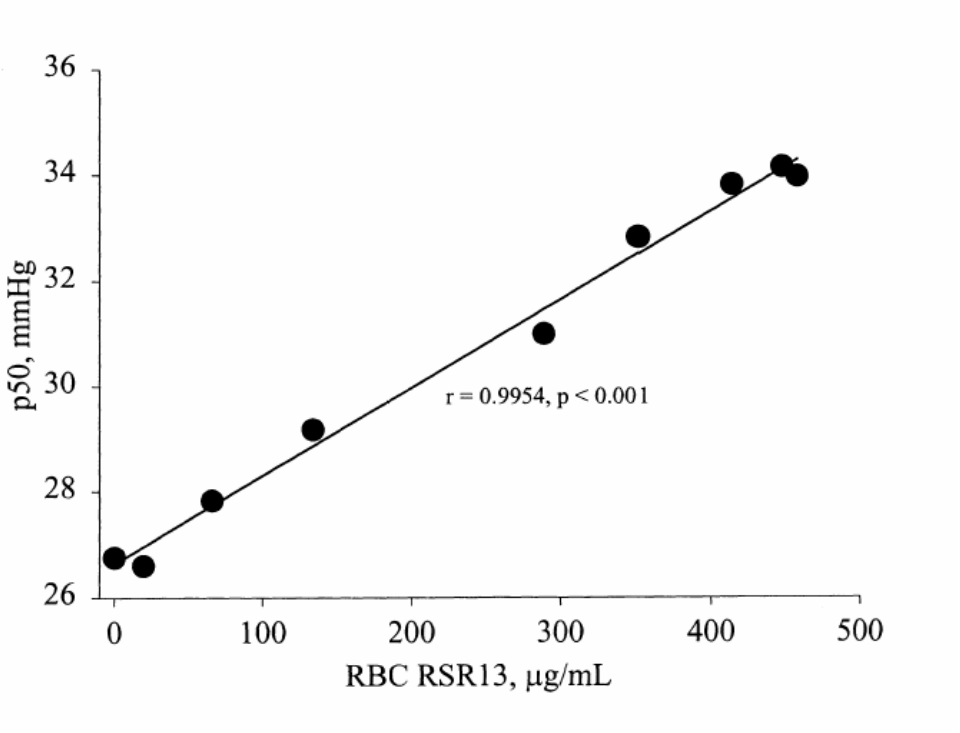


The first clinical study of RSR13, HV-001, was a randomized, double-blind, placebo-controlled, single-center, partial crossover study employing single, sequential, ascending RSR13 doses administered by IV infusion to 19 healthy subjects (16 male, 3 female). RSR13 pharmacokinetics (PK) was evaluated at 4 of the 5 ascending doses of 10 (kinetics not measured at this dose), 25, 50, 75, and 100 mg/kg. The predefined pharmacodynamic endpoint was a p50 shift of 10 mmHg and was consistently achieved at a dose of 100 mg/kg. Therefore, it was concluded that the doses necessary to achieve a p50 shift of 10 mmHg could be administered to healthy volunteers.

Study RT-002 followed as the first study with RSR13 as an adjunct to RT in cancer patients. RT-002 was a non-randomized, open-label, multi-center study in which RSR13 was administered with supplemental oxygen immediately prior to RT in patients with histologically or cytologically proven malignancy refractory to, or not amenable to, curative anticancer therapy. Patients were to receive a 2-3 week course of palliative RT. RSR13 was administered by constant-rate, IV infusion at doses of 75 or 100 mg/kg over 60 minutes. The first RSR13 dose was started on or before the patient's fourth radiation treatment. The objectives of the study were to evaluate the safety/tolerability of escalating the RSR13 dose, as well as to determine the

PK/PD profile. The pharmacodynamic (PD) endpoint of the study was a targeted increase in p50 of 10 mmHg. The results of the study showed RSR13 concentration in red blood cells (RBCs) correlates strongly with the PD activity (Figure 2.2). The effect of RSR13 in oncology patients was the same as the effect in healthy volunteers.

Figure 2.2
RBC RSR13 Concentration versus p50 for Patients who Received RSR13 at 100 mg/kg in Study RT-002 (Kavanagh et al., 2001)



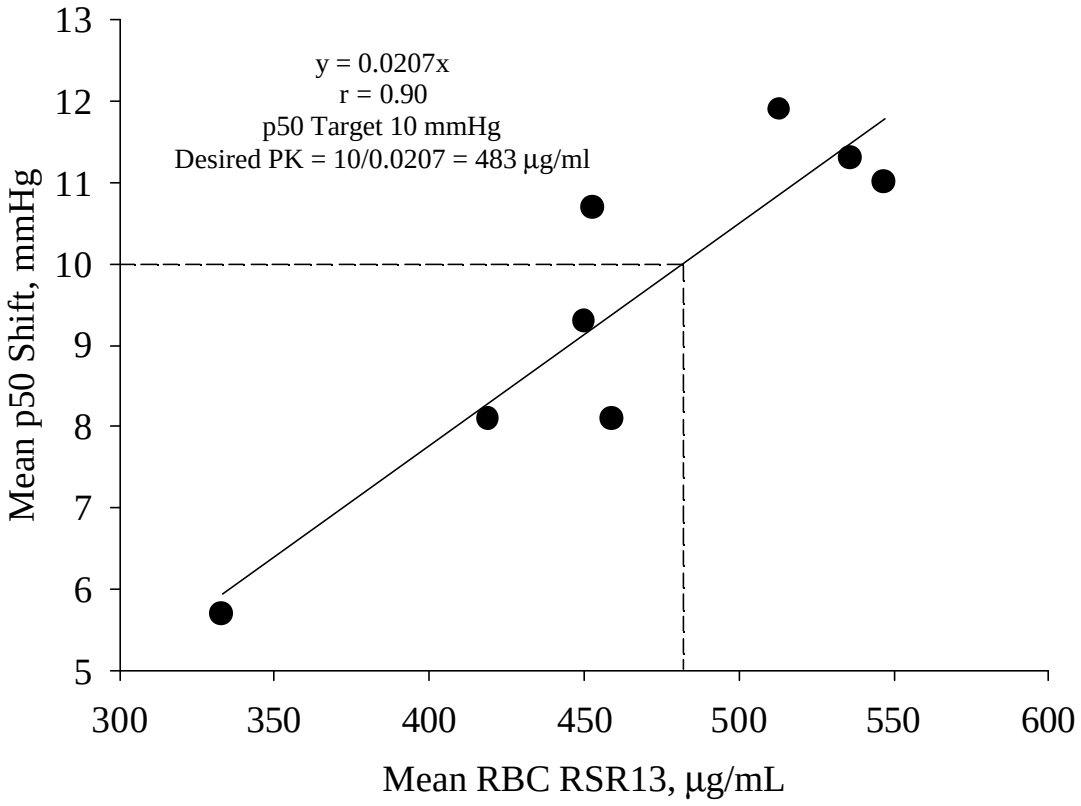
Further data supporting the correlation of RSR13 dose, PK and PD data are presented in Table 2.3 and Figure 2.3.[23-30] The data are from all RSR13 studies with PK/PD data obtained at both 75 and 100 mg/kg (HV-001, RT-002, RT-008, and RT-010). The data show that an RSR13 dose of 100 mg/kg can produce RSR13 RBC concentrations that correlate with the desired p50 shift. Figure 2.3 demonstrates 1) that increasing RSR13 RBC concentration correlates with increasing p50, and 2) to achieve the desired PD effect, an RSR13 RBC concentration of at least 483 µg/mL in RBCs has to be reached.

Table 2.3
RSR13 Dose, PK, and PD Data[a]

Population (study identification)	N	Infusion Duration (minutes)	Dose (mg/kg)	Mean RSR13 concentration in RBCs (mg/mL)*	Mean p50 Shift
Healthy subjects (HV-001)[29-31]	24	60	75	450	9.3
			100	513	11.9
Patients with solid tumors of different types (RT-002)[27]	20	60	75	333	5.7
			100	459	8.1
Brain metastases (RT-008)[23]	69	30	75	453	10.7
			100	536	11.3
NSCLC (RT-010)[24-26]	47	30	75	419	8.1
			100	547	11.0

N: number of patients who received at least 1 RSR13 dose
Mean maximum concentration (C_{max}) occurring at end-infusion
[a]Correlation includes studies in which the pharmacokinetic/pharmacodynamic data were obtained at doses of 75 and 100 mg/kg.

Figure 2.3
Correlation of RSR13 Pharmacokinetics/Pharmacodynamics



2.2.2.1 RSR13 Clinical Pharmacokinetic Summary

The PK of RSR13 were **consistent** across all studies and the PK results at therapeutic doses are summarized below:

- Low mean clearance (<1 mL/min/kg).
- Low steady-state volume of distribution (<0.2 L/kg).
- Plasma protein binding is ~95% and saturable.
- Saturable plasma protein binding increases the RBC/plasma concentration ratio, presumably by permitting relatively more unbound drug to penetrate the RBCs.
- Terminal exponential half-lives ~5.6 hours and 4.5 hours in plasma and RBCs, respectively.
- All metabolism occurs via conversion (conjugation) to acyl glucuronide (RSR13AG), a saturable metabolic process.
- RSR13 is eliminated predominantly via renal excretion (83%) (HV-003). RSR13 is excreted as intact RSR13 or as RSR13AG, through passive filtration and saturable and active tubular secretion.
- Minimal drug accumulation occurs on once daily administration for 5 consecutive days.

2.2.2.2 RSR13 Clinical Pharmacodynamic Summary

The PD activity of RSR13 (increase in p50) was **consistent** across all studies and corresponds with the pharmacokinetics of RSR13. The PD results at therapeutic doses are summarized below:

- The key PD measurement of RSR13 activity is the partial pressure of oxygen which results in a 50% saturation of hemoglobin (p50).
- RSR13 concentration in RBCs strongly correlates with the PD activity (Figures 2.2 and 2.3).
- RSR13 dosing is not based on achieving steady-state, but rather is necessary only for a period of time needed to administer the RT.
- All PD activity derives from intact RSR13; RBCs are impervious to RSR13AG, presumably due to its hydrophilic nature.

2.2.2.3 RSR13 Dose Justification

Studies showed that an increase in p50 of 10 mmHg provided for oxygen dissociation while still allowing sufficient cooperativity to assure sizable saturation in the pulmonary circulation. This should provide adequate oxygen gradient to enhance tumor oxygenation and radiation sensitization. Studies HV-001 and RT-002 determined that a dose of 100 mg/kg was feasible, well tolerated, and consistently achieved an RSR13 concentration in RBCs that correlated with the desired PD effect.

3.0 PIVOTAL PHASE 3 STUDY FOR THE TREATMENT OF PATIENTS WITH BRAIN METASTASES (RSR13 RT-009)

3.1 Study Design

Study RT-009 was a randomized, open-label, comparative, multi-center, efficacy, safety, and PK study in patients receiving a standard 2-week course of WBRT for brain metastases with RSR13 (RSR13 arm) or without RSR13 (Control arm). Patients in both treatment arms were randomized to receive WBRT, 30 Gy in 10 daily fractions of 3.0 Gy, as well as supplemental oxygen at 4 L/min via nasal cannula beginning 35 minutes prior to, during, and for at least 15 minutes after completion of daily WBRT. The RSR13-treatment group received RSR13 at 100 or 75 mg/kg (depending on the dosing algorithm) administered via central venous access by volumetric pump over a 30-minute interval no more than 30 minutes prior to each session of a 10-day course of WBRT.

The MST for the Control arm was estimated to be 4.57 months. The alternative hypothesis was that WBRT (plus supplemental oxygen) with RSR13 improves survival. A sample size of 239 eligible patients per treatment arm provided overall statistical power of 85% (assuming an increase of MST of 35%) with a two-sided significance value of 0.05. The estimated sample size included the following parameters: shape parameter of 0.0 (O'Brien and Fleming), and 27 months of accrual at 17.67 patients per month. A minimum of 402 deaths was required for analysis of survival. Amendment 2 added the co-primary population of NSCLC/breast for the survival analysis; a minimum of 308 deaths was required for analysis.

Enrolled patients had to have histologically or cytologically confirmed brain metastases, or radiographic studies consistent with brain metastases. Study RT-009 was open-label and unblinded. The patients and the investigative staff could not be blinded because RSR13 can produce hypoxemia. The Control arm did not receive a placebo because RSR13 must be administered through a CVAD.

Patients were stratified at randomization to the following:

1. RPA Class I
2. RPA Class II NSCLC primary
3. RPA Class II breast primary
4. RPA Class II with other primaries

Definitions of RPA classes are provided in Table 1.1. In study RT-009, each patient was centrally randomized prior to the planned commencement of WBRT. Patients were randomized (within assigned stratum) 1:1 to the 2 treatment arms based on a modified balanced block randomization.[32]

The main eligibility criteria for inclusion are listed below. Eligibility for enrollment was determined at the screening visit and reassessed at baseline for confirmation. Enrollment was open to male and female patients of any ethnic background. Females and minorities were actively recruited for this protocol.

Eligibility

(1) Radiographic studies consistent with brain metastases and a histologically or cytologically confirmed primary malignancy, excluding small cell lung cancer and extrapulmonary small cell carcinomas, germ cell tumors, and lymphomas; or histologically or cytologically confirmed brain metastases consistent with a non-excluded primary malignancy. Patients with leptomeningeal metastases were not eligible.
(2) ≥18 years of age and able to provide written informed consent.
(3) No prior treatment for brain metastases with the exception of prior surgical resection if at least 1 measurable lesion remained; prior and concurrent corticosteroid therapy allowed.
(4) Adequate hematologic, renal, hepatic, and pulmonary function as determined by screening physical examination, pulmonary function tests, and laboratory measurements.
(5) Resting and exercise standard pulse oximetry (SpO_2) while breathing room air ≥90%.
(6) No cytotoxic chemotherapy within 7 days prior to WBRT day 1, scheduled during the WBRT course or for 1 month after completion of WBRT.
(7) No use of any investigational drug, biologic, or device within 4 weeks prior to WBRT day 1.
(8) Negative serum beta-human chorionic gonadotropin pregnancy test at screening and practicing a medically acceptable contraceptive regimen, if patient a female of childbearing potential.
(9) Karnofsky performance status (KPS) ≥70.
(10) Patients must not have previously received RSR13.

3.1.1 Study Endpoints

The primary endpoint was survival and the secondary efficacy endpoints (Table 3.1) were response rate in the brain, time to radiographic tumor progression and time to clinical tumor progression in the brain, cause of death, and quality of life (QOL).

Table 3.1
Description of the Secondary Endpoints in Study RT-009

Response Rate in the Brain	Scheduled radiographic assessments of indicator lesions at 1 and 3 months after RT course; every 3 months thereafter compared to baseline
Time to Radiographic Tumor Progression in the Brain	Any treated lesion in the brain was enlarged by >25%
Time to Clinical Tumor Progression in the Brain	Assessment was made using: 1. Neurologic Function (NF) Status score 2. Mini-mental State Exam (MMSE)
Cause of Death	Determined as neurologic, non-neurologic, or indistinguishable
QOL	KPS and Spitzer Questionnaire

3.1.2 Prespecified Plans for Analysis of Results

Analysis of the primary endpoint (survival) was based on the assumptions listed in Table 3.2.

Table 3.2
Assumptions for the Primary Endpoint

RPA Class I : II	20% : 80%
MST Control arm	4.57 months
35% Improvement	6.17 months in the RSR13 arm
Number of events (deaths)	402 All randomized patients 308 NSCLC/breast patients 6-month minimum follow-up

Due to the heterogeneity of these patients, and the potential for imbalances in prognostic factors, the Cox multiple regression model was specified in the protocol and statistical analysis plan (SAP). Table 3 3 lists all prespecified Cox model baseline covariates.

Table 3.3
Prespecified Cox Model Baseline Covariates in Study RT-009

Prespecified in the RT-009 Protocol	Prespecified and Added in the RT-009 SAP
RPA Class Primary tumor type Control of primary Age Extent of extracranial metastases KPS Number of brain metastases	Gender Hemoglobin Presence of liver metastases Size of brain metastases Previous resection of brain metastases Timing of diagnosis Site location Site size Altitude Weight category

Based on the literature, the anticipated 402 events are adequate to allow for up to 40 covariates. Since only 17 covariates were specified, the assumption for number of events per covariate was adequately met.[33]

In Table 3.3, timing of diagnosis was defined per SAP as synchronous (less than 30 days between diagnosis of primary and brain metastases) versus metachronous (30 days or more between the diagnosis of primary and brain metastases).

To ensure that results of the Cox analysis were not sensitive to the functional form of the covariates, 5 covariates were considered in more than one way. These included age, KPS, area of brain metastases, hemoglobin, and altitude. This resulted in a possible 48 unique Cox models. In addition, both the full model (all covariates in model simultaneously) and the stepwise selection model were specified.

The SAP defined, per strict International Committee on Harmonization (ICH) guidelines, the eligible patient population as the primary analysis population. Efficacy analyses were also performed on all randomized patients. In both cases, the 2 co-primary populations were analyzed. In addition, the results were analyzed per stratum and by site of primary (regardless of RPA classification).

3.1.3 Protocol Amendments

A total of 3 amendments were brought to the original study protocol. All changes dealt with logistical and administrative aspects of the study or minor clarification of wording with the exception of the following changes summarized in Table 3.4.

Table 3.4
Summary of Protocol Amendments for Study RT-009

Amendment (Protocol Version)	Date	Description of Change
Amendment 1 (Protocol Version 2)	02 Mar 2000	• Expand MRI/CT specifications • Omit RSR13 on any day if SpO_2 <90%
Amendment 2 (Protocol Version 3)	05 Jun 2001	• Sample size up to 538 patients with NSCLC/breast co-primary • Dose Adjustment for anti-hypertensives, weight, and gender
Amendment 3 (Protocol Version 4)	09 Oct 2001	• Use of Cobalt 60 allowed

Based on the higher percentage of dosing terminations early on in the course of study RT-009 relative to RT-008, as well as the approximate PK target of 500 µg/mL, we modeled the RSR13 RBC concentrations at end-infusion prior to amendment 2 using dose, gender, and weight as independent variables. The mixed model results suggested that heavy patients of either sex could be overdosed at 100 mg/kg. Based on the model results, a cutoff weight for each sex that predicted an end-infusion RBC concentration of approximately 500 µg/mL was determined and then adjusted downward to ensure patients would not be overdosed on their initial dose of RSR13. While this algorithm was intended to only affect the initial dose of RSR13 for heavy patients, the practical result was that investigators did not always increase the dose of RSR13 to 100 mg/kg after day 1 even in the absence of safety concerns, thereby not allowing for the maximum therapeutic benefit of RSR13. In addition, this conservative approach to RSR13 dosing was applied in many cases to low weight patients, and when added to the existing dosing guidelines led to higher rates of RSR13 doses held and reduced in protocol Versions 3 and 4.

3.2 Patient Demographics, Baseline Characteristics and Efficacy Results

3.2.1 Patient Demographics and Baseline Characteristics

Patients were randomized from 82 investigational sites in 12 countries. The first patient consent was received on 16 Feb 2000 and the date of the last initial (1-month) follow-up was 24 Sep 2002. A total of 538 patients were planned (269 in each treatment arm): 538 patients total were randomized (Control arm: 267 patients; RSR13 arm: 271 patients), and 515 met the eligibility criteria (Control arm: 250 patients; RSR13: 265 patients). Table 3.5 lists the

23 patients who failed to meet disease specific eligibility criteria; these patients did not conform to the basic definition of the study population. All except 1 patient with small cell lung cancer were identified through independent central review of the scans blinded to study arm and treatment outcome.

Table 3.5
Ineligible Patients Identified by Blinded Central Review of Scans

Reason Ineligible	Primary Site	Control N = 17	RSR13 N = 6
Leptomeningeal metastases	NSCLC	5	3
	Breast	3	2
	Other	4	1
No measurable brain lesions (status post-resection)	NSCLC	1	0
	Breast	2	0
Small cell lung cancer	Other	1	0
Dural disease related to skull metastases	Breast	1	0

There were 529 patients who received at least on1 dose of protocol-specified study treatment (Control arm: 263 patients; RSR13 arm: 266 patients) and were therefore analyzed for safety.

Demographics are presented in Table 3.6. Overall, demographics were similar between the 2 treatment arms but with a slight trend towards younger patients in the Control arm.

Because body weight was a determinant for the starting dose of RSR13 after Amendment 2, analysis was performed to show body weight by gender and primary site subpopulation. Per protocol females >70 kg and males >95 kg were grouped in the high body weight (HW) category and females ≤70 kg and males ≤95 kg were classified as low body weight (LW). In the RSR13 arm, most patients in the NSCLC primary subpopulation were LW (83%) while in the breast primary subpopulation, only 47% of patients were LW. Mean body weight for females in the breast primary subpopulation was 4 kg higher than the mean body weight for females in the NSCLC primary subpopulation and 3 kg higher than the overall mean body weight for the subpopulation of patients with NSCLC primary. In the Control arm, the same trend was observed.

Table 3.6
Summary of Demographic Data in Control and RSR13 Treated Patients, Efficacy Oncology Studies

Parameter	RT-009 Control (N = 267)	RT-009 RSR13 (N = 271)
Gender n (%)		
Male	117 (44)	118 (44)
Female	150 (56)	153 (56)
Race n (%)		
Caucasian	239 (90)	242 (89)
Black	12 (4)	15 (6)
Native American	1	1
Asian	3 (1)	2 (1)
Hispanic	6 (2)	7 (3)
Other/Missing	6 (2)	4 (2)
Age (years)		
<65 years n (%)	197 (74)	196 (72)
≥65 years n (%)	70 (26)	75 (28)
Mean	57.0	57.1
SD	11.0	11.1
Min-Max	23—81	30—87
Weight (kg)		
Mean	72.5	71.3
SD	17.1	15.0
Min-Max	33.0—140.9	39.8—122.0
n Missing	2	0
Weight Category[a]		
LW	198 (74)	204 (75)
HW	67 (25)	67 (25)
Strata as Randomized		
Stratum 1: RPA Class I	28 (10)	29 (11)
Stratum 2: RPA Class II – NSCLC primary	132 (49)	132 (49)
Stratum 3: RPA Class II – Breast cancer primary	51 (19)	52 (19)
Stratum 4: RPA Class II – Other primary tumor type	56 (21)	58 (21)
Screening Resting SpO_2[b]		
<96%	53 (20)	59 (22)
≥96%	214 (80)	212 (78)

[a]Two patients had missing data in the Control arm.
[b]Missing baseline resting SpO_2 counted in the <96% category.

Tumor history is summarized by treatment arm in Table 3.7. There were imbalances in several important prognostic factors, all of which favored the Control arm, including: the proportion of patients without extracranial metastases, the proportion of patients without liver metastases, the proportion of patients with a prior brain tumor resection, and the time from diagnosis of primary disease to study day 1 (ie, WBRT day 1).

Table 3.7
Tumor History and Extent of Disease by Treatment Arm in Study RT-009

Covariate	Value	Control N = 267	RSR13 N = 271
RPA Class:	I	28	29
	II	239	242
Primary Control:	Controlled	67	72
	Uncontrolled	200	199
Duration of primary disease (months)[a]:	Q1	1.1	0.9
	Q2	11.4	9.9
	Q3	33.8	28.9
Presence of extracranial metastases:	Yes	171	187
	No	96	84
Prior treatment for brain metastases:	Yes	29	21
	No	238	250
Liver metastases:	Yes	42	54
	No	225	217

[a]Q1, Q2, and Q3 represent the first, second, and third quartiles, respectively

3.2.2 Dosing

The selection of the RSR13 doses administered in this study was based on the safety and efficacy results obtained in the Phase 2 open-label studies in which over 270 cancer patients (including 69 patients with brain metastases) received repetitive daily RSR13 infusions prior to RT. Based on these background data, the starting dose in this present study was 75 or 100 mg/kg.

The changes in the initial RSR13 dose received as a result of Amendment 2 (Protocol Version 3) are summarized in Table 3.8.

Table 3.8
Dosing Guidelines by Protocol Version

	Protocol Versions 1 and 2	Protocol Versions 3 and 4
SpO_2 <90%	RSR13 held	RSR13 held
SpO_2 90%-92%	RSR13 administered at 75 mg/kg	RSR13 administered at 75 mg/kg
SpO_2 ³93%	RSR13 administered at 100 mg/kg	The following weight and gender guideline was used: Males - If weight ≤95 kg, administer 100 mg/kg RSR13 - If weight > 95 kg, administer 75 mg/kg RSR13 Females - If weight ≤70 kg, administer 100 mg/kg RSR13 - If weight > 70 kg, administer 75 mg/kg RSR13

Under Protocol Versions 3 and 4, if a patient was administered anti-hypertensive medications the patient received RSR13 at 75 mg/kg.

Reasons for dose reductions for Protocol Versions 1-4 can be summarized as follows:

(1) Supplemental oxygen was administered for >3 hours
(2) Nausea and/or vomiting ≥Grade 2
(3) Hypotension
(4) Hypoxemia requiring treatment after discharge
(5) Room air SpO_2 90%-92% with ≥93% on previous day

The number of RSR13 doses and the mean RSR13 dose administered during the study are summarized in Table 3.9. Fifty-two percent (141/271) of RSR13-treated patients received the entire RSR13 course of 10 doses. The majority of patients (80%, 218/271) received 7 or more RSR13 doses, and only 13% (34/271) of patients received ≤4 RSR13 doses. RSR13 did not affect the delivery of WBRT.

Table 3.9
Number of WBRT and RSR13 Doses Received by Treatment Arm, Study RT-009

Number of Doses	Control N = 267	RSR13 N = 271	
	WBRT N (%)	WBRT N (%)	RSR13 n (%)
0	4 (1)	5 (2)	8 (3)
1-6	6 (2)	9 (3)	45 (17)
7-9	3 (1)	3 (1)	77 (28)
10	254 (95)	254 (94)	141 (52)
Mean	9.9	9.8	8.4

3.2.3 Efficacy Results

The study RT-009 efficacy results are organized as follows:

3.2.3.1 Overview of Key Efficacy Findings

Key Efficacy Findings Overall:

- 38% increase in MST and an 18% reduction in risk of death observed in the co-primary population of eligible NSCLC/breast patients (HR [hazard ratio] = 0.82, p = 0.07, unadjusted log-rank) in the per-protocol January 2003 analysis. This estimate became more precise with the additional follow-up conducted in January 2004 (HR = 0.82, p = 0.05, unadjusted log-rank).
- 13% reduction in risk of death observed in the co-primary population of all eligible patients (January 2003 analysis: HR = 0.87, p = 0.16, unadjusted log-rank; January 2004 analysis: HR = 0.87, p = 0.13, unadjusted log-rank).
- 24% reduction in risk of death observed in both co-primary populations after correcting for the imbalances in prognostic factors via the prespecified Cox multiple regression model (p = 0.01 and p = 0.02 in all eligible and all eligible NSCLC/breast co-primary populations, respectively).
- Survival advantage due to RSR13 driven by the patients with breast primary; 45% reduction in risk of death observed in these patients (HR = 0.55, p <0.01, unadjusted log-rank).
- Survival advantage due to RSR13 in co-primary NSCLC/breast population as well as breast primary patients supported by increased response rate (Control vs RSR13 response rate: 41% vs 53% [p = 0.01] in NSCLC/breast patients and 49% vs 72% [p = 0.02] in breast patients).

Key Efficacy Findings in Breast Cancer Patients:

- 90% improvement in MST (4.6 vs 8.7 months, HR = 0.55, 95% confidence interval (CI): 0.35, 0.85)
- Consistent treatment effect on response rate and QOL
- Treatment arms well-balanced by prespecified covariates and subsequent therapy

3.2.3.2 Primary Endpoint: Survival

The SAP specified that the primary survival analysis was to be performed using the unadjusted log-rank test on 2 populations: all eligible patients and all eligible NSCLC/breast patients. In addition, the protocol stated that analysis of all randomized patients in the 2 co-primary populations and an analysis by stratum would be performed. Furthermore, to correct for potential imbalances in prognostic factors between the treatment arms, a Cox model was fully prespecified in the SAP.

For the original data analyses, overall survival was calculated from the time of randomization into the study until death or 31 Jan 2003, whichever occurred first. At the time of this survival analysis, there were a total of 441 deaths in the entire patient population and 331 in the NSCLC/breast population. A survival follow-up was conducted with survival data until January 2004, which provided an additional 12 months of data. At this update, there were a total of 496 deaths in the entire patient population and 377 in the NSCLC/breast population.

The RT-009 study protocol and the SAP specified log-rank as the primary statistical test to be applied to the survival analyses, but an argument can be made that the log-rank test is not the most appropriate tool to analyze the survival results of study RT-009. It has been demonstrated in simulation studies, and verified in study RT-009, that for heterogeneous samples a simple log-rank test can yield misleading results.[35] In addition, slight imbalances in known prognostic factors can bias treatment comparisons as reviewed by Sather et al[36] and by Altman et al.[37]

For all of the covariates listed in Table 3.3, the proportional hazards assumption underlying the Cox multiple regression models was examined and verified using a nonparametric kernel smoothing plot of the hazards.[34] Notably, the hazard functions generally declined with time. A deviance residual plot showed that the results of the analysis were robust with respect to outliers. Furthermore, the RSR13 estimates were consistent regardless of the functional form of the covariates as outlined in Section 3.1.2.

Unless otherwise noted, all survival analysis results represent the analysis at the protocol specified time, conducted using follow-up through January 2003.

3.2.3.2.1 Survival in All Eligible Patients

The observed MST for the Control arm (N = 250) was 4.4 months compared to 5.4 months for the RSR13 arm (N = 265) (Figure 3.1). This treatment effect translated into a hazard ratio of 0.87 via the unadjusted log-rank test ($p = 0.16$) and a hazard ratio of 0.76 via the prespecified Cox multiple regression model utilizing all covariates simultaneously ($p < 0.01$). The reason for the discrepancy between the 2 tests is primarily due to the imbalance in important prognostic factors between the 2 treatment arms; namely, KPS, and the presence of extracranial metastases (Table 3.10). Beginning with a Cox model that included only treatment arm, Table 3.11 shows how adding covariates one-at-a-time based on their statistical significance in the full Cox model affects the RSR13 treatment effect estimate. After adjusting for the imbalances in KPS and presence of extracranial metastases, the 2 most significant covariates in the full Cox model, the RSR13 treatment effect has a p-value of 0.03.

Figure 3.1
Kaplan-Meier Survival Curve for All Eligible Patients
RSR13 Arm (N = 265) versus Control Arm (N = 250)

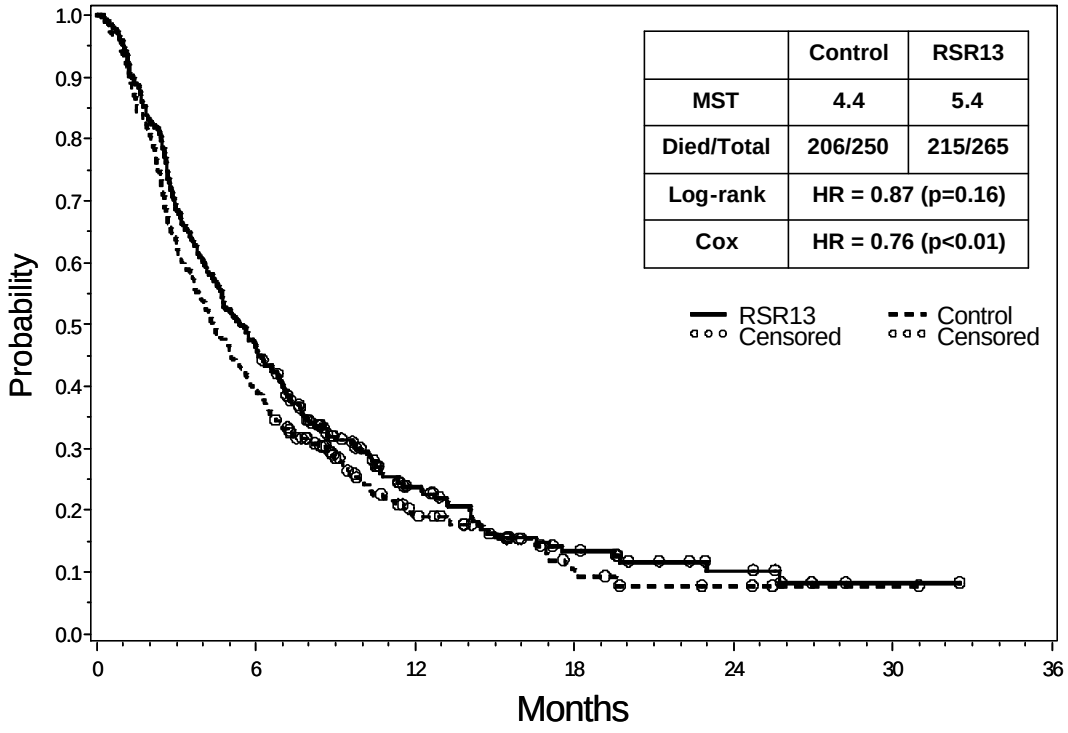


Table 3.10
Distribution of Prognostic Factors by Treatment Group, All Eligible Patients in Study RT-009

Covariate	Value	Control (N = 250) %	RSR13 (N = 265) %
Primary Site	NSCLC	58	55
	Breast	20	22
	Other	22	23
Age	<65 years	73	72
	≥65 years	27	28
Baseline KPS	100	16	13
	90	37	46
	80	31	23
	70	16	17
Gender	Female	56	56
	Male	44	44
Control of primary cancer	Controlled	24	26
	Uncontrolled	76	74
RPA Class	I	10	11
	II	90	89
Number of sites of extracranial metastases	0	36	31
	1 to 2	46	48
	≥3	18	22
Presence of liver metastases	Yes	16	20
	No	84	80
Number of brain metastases [a]	1	20	17
	2 to 3	32	30
	>3	47	52
Sum of Bidimensional products of lesions [a]	<250 mm^2	25	26
	250-1000 mm^2	46	50
	>1000 mm^2	28	23
Timing of Diagnosis	Metachronous	68	67
	Synchronous	32	33
Prior cranial tumor resection	Yes	10	8
	No	90	92
Baseline hemoglobin	<12 g/dL	16	17
	≥12 g/dL	84	83
Site location	USA	47	50
	Canada	32	29
	ROW	21	21
Altitude at treatment site	<2000 feet	86	87
	≥2000 feet	14	13
Weight per dosing adjustment algorithm	High weight	26	25
	Low weight	74	75

[a] Five patients with missing data

Table 3.11
Treatment Effect Correcting for Imbalances, All Eligible Patients[a]

Covariates in Cox Model	RSR13 Effect
---	HR = 0.87, p = 0.16
KPS	HR = 0.86, p = 0.12
KPS, Number of Extracranial Metastases	HR = 0.81, p = 0.03
KPS, Number of Extracranial Metastases, Prior resection	HR = 0.80, p = 0.02
KPS, Number of Extracranial Metastases, Prior resection, Gender	HR = 0.78, p = 0.01
KPS, Number of Extracranial Metastases, Prior resection, Gender, Breast Primary	HR = 0.79, p = 0.02
KPS, Number of Extracranial Metastases, Prior resection, Gender, Breast Primary, Age Group	HR = 0.79, p = 0.01

[a]Last row contains all covariates that were statistically significant ($p < 0.05$)

For the initial survival data analyses, overall survival was calculated from the time of randomization into the study until death or 31 Jan 2003, whichever occurred first. The survival results were updated through January 2004. There were 474 deaths in the updated survival data. The unadjusted hazard ratio for the updated survival data was 0.87 (95% CI: 0.72, 1.05) and the Cox multiple regression HR was 0.79 (95% CI: 0.65, 0.95).

3.2.3.2.2 Survival in All Eligible Patients in the NSCLC/breast Population

The observed MST for the Control arm (N = 194) was 4.4 months compared to 6.0 months for the RSR13 arm (N = 203) (Figure 3.2). This treatment effect translated into a hazard ratio of 0.82 via the unadjusted log-rank test ($p = 0.07$) and a hazard ratio of 0.76 via the prespecified Cox multiple regression model utilizing all covariates simultaneously ($p = 0.02$). The reason the Cox multiple regression model results in a lower p-value is primarily due to the slight imbalance in important prognostic factors between the 2 treatment arms; namely, KPS and prior brain tumor resection (Table 3.12). Beginning with a Cox model that included only treatment arm, Table 3.13 shows how adding covariates one-at-a-time based on their statistical significance in the full Cox model affects the RSR13 treatment effect estimate. After adjusting for KPS and presence of extracranial metastases, the 2 most significant covariates in the full Cox model, the RSR13 treatment effect has a p-value of 0.03.

Figure 3.2
Kaplan-Meier Survival Curve for All Eligible NSCLC/breast Patients
RSR13 Arm (N = 203) versus Control Arm (N = 194)

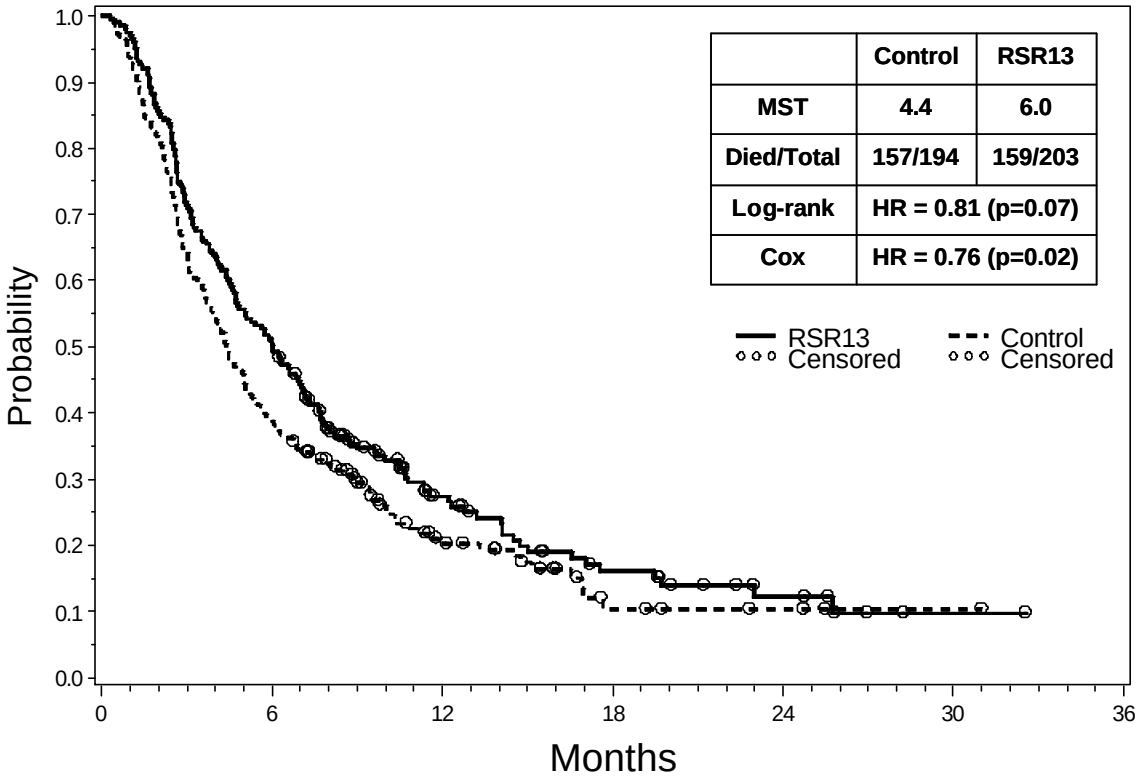


Table 3.12
Distribution of Prognostic Factors by Treatment Group, Eligible NSCLC/breast Patients in Study RT-009

Covariate	Value	Control (N = 194) %	RSR13 (N = 203) %
Primary Site	NSCLC	75	71
	Breast	25	29
Age	<65 years	72	72
	≥65 years	28	28
Baseline KPS	100	16	13
	90	39	47
	80	28	24
	70	16	17
Gender	Female	62	61
	Male	38	39
Control of primary cancer	Controlled	23	23
	Uncontrolled	77	77
RPA Class	I	10	11
	II	90	89
Number of sites of extracranial metastases	0	37	36
	1 to 2	46	46
	≥3	18	17
Presence of liver metastases	Yes	15	15
	No	85	85
Number of brain metastases [a]	1	21	18
	2 to 3	30	32
	>3	48	49
Sum of bidimensional products of lesions [a]	<250 mm^2	25	26
	250-1000 mm^2	46	48
	>1000 mm^2	29	25
Timing of Diagnosis	Metachronous	67	63
	Synchronous	33	37
Prior cranial tumor resection	Yes	8	5
	No	92	95
Baseline hemoglobin	<12 g/dL	16	13
	≥12 g/dL	84	87
Site location	USA	45	49
	Canada	34	30
	ROW	21	21
Altitude at treatment site	<2000 ft	86	89
	≥2000 ft	14	11
Weight per dosing adjustment algorithm	High weight	26	28
	Low weight	74	72

[a] Three patients with missing data

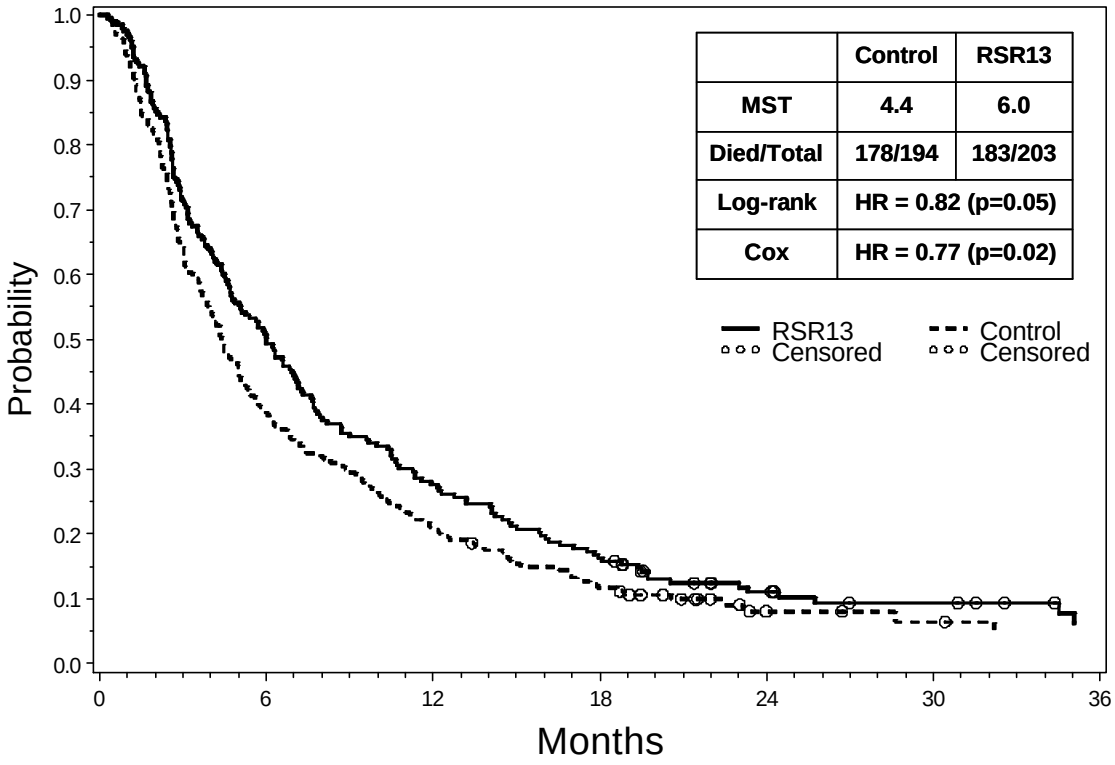
Table 3.13
Treatment Effect Correcting for Imbalances, All Eligible NSCLC/breast Patients[a]

Covariates in Cox Model	RSR13 Effect
---	HR = 0.82, p = 0.07
KPS	HR = 0.80, p = 0.05
KPS, Number of Extracranial Metastases	HR = 0.78, p = 0.03
KPS, Number of Extracranial Metastases, Age	HR = 0.78, p = 0.03
KPS, Number of Extracranial Metastases, Age, Prior resection	HR = 0.77, p = 0.02
KPS, Number of Extracranial Metastases, Age, Prior resection, Gender	HR = 0.75, p = 0.01

[a]Last row contains all covariates that were statistically significant ($p < 0.05$)

There were 361 deaths in the survival data updated through January 2004. The unadjusted hazard ratio for the updated survival data was 0.82 (95% CI: 0.66, 1.00) and the Cox adjusted HR was 0.77 (95% CI: 0.62, 0.95). Importantly, the difference in survival for the co-primary population of eligible patients with NSCLC/breast cancer reaches p = 0.05 before correcting for the imbalances in prognostic factors, as shown by Figure 3.3. Also, the results of the unadjusted log-rank and Cox multiple regression model are roughly consistent (HR = 0.82, p = 0.05 vs HR = 0.77, p = 0.02, respectively).

Figure 3.3
Kaplan-Meier Survival Curve for All Eligible NSCLC/breast Patients
RSR13 Arm (N = 203) versus Control Arm (N = 194)
January 2004

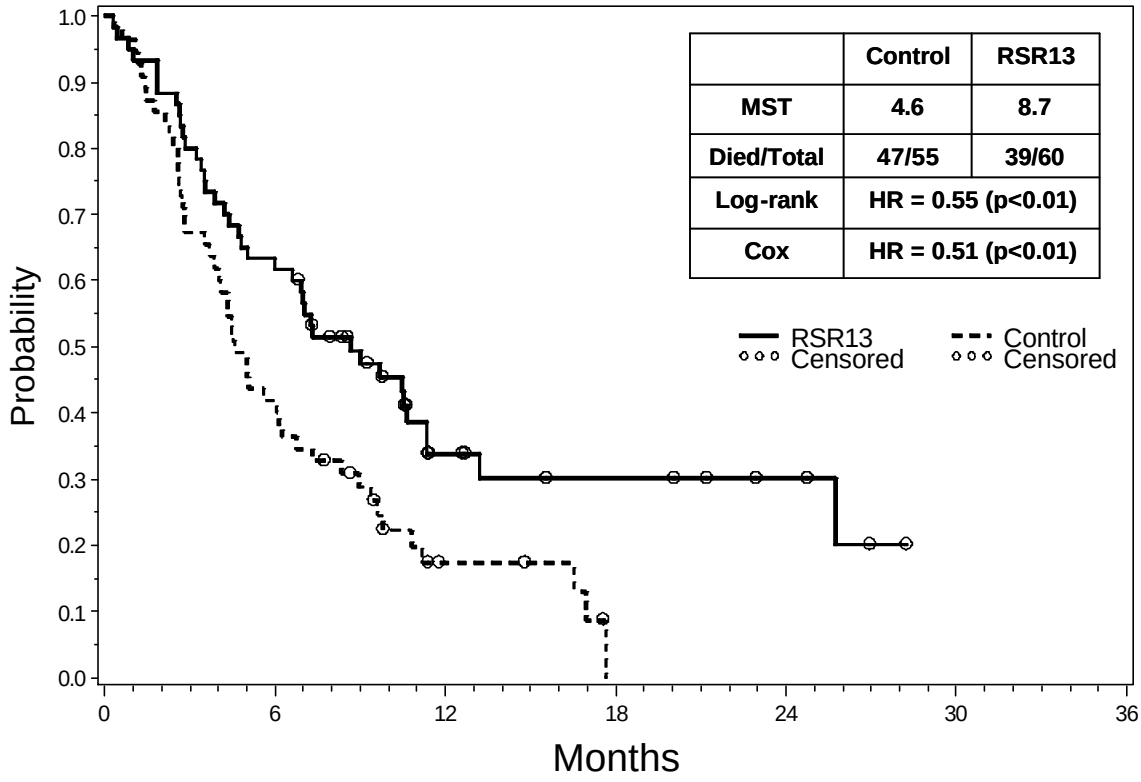


3.2.3.2.3 Survival in Patients with Breast Cancer

Based on the survival difference between treatment arms in the survival data for all eligible NSCLC/breast patients, and due to the fact that breast cancer patients represent a distinct population, we then analyzed the results of all breast cancer patients to determine if there was a different treatment effect in the 2 tumor types comprising this co-primary population; namely, NSCLC and breast.

In the breast cancer patients, the observed MST for the Control arm (N = 55) was 4.6 months compared to 8.7 months for the RSR13 arm (N = 60) (Figure 3.4). This treatment effect translated into a hazard ratio of 0.55 via the unadjusted log-rank test ($p < 0.01$) and a hazard ratio of 0.51 via the prespecified Cox multiple regression model utilizing all covariates simultaneously ($p < 0.01$).

Figure 3.4
Kaplan-Meier Survival Curve for All Randomized Patients with Breast Cancer Primary RSR13 Arm (N = 60) versus Control Arm (N = 55)



As stated in the Cox single regression model (as well as above), a highly statistically significant difference could be determined for RSR13 effect between the treatment arms without adjustments for covariates ($p < 0.01$). Patients who received RSR13 had a 45% reduction in the likelihood of death at a given time-point than patients in the Control arm (HR = 0.55, 95% CI: 0.35, 0.85).

The analysis in Table 3.14 shows consistent results for breast cancer primary patients across all prespecified covariates.

Table 3.14
Covariate Analysis for Breast Cancer Patients in Study RT-009

Covariate	Value	Control		RSR13		Hazard Ratio
		%	MST	%	MST	(95% CI)
Age	<65 years	82	6.05	80	10.48	0.55 (0.34, 0.90)
	≥65 years	18	2.78	20	5.70	0.35 (0.12, 0.98)
Baseline KPS	90 - 100	56	7.29	60	10.64	0.58 (0.32, 1.05)
	<90	44	2.79	40	5.70	0.52 (0.28, 0.98)
Control of primary cancer	controlled	33	6.42	32	11.33	0.54 (0.23, 1.26)
	uncontrolled	67	4.47	68	7.26	0.53 (0.32, 0.87)
RPA Class	I	11	12.94	13	25.72	0.37 (0.07, 2.01)
	II	89	4.47	87	7.03	0.56 (0.36, 0.88)
Number of sites of extracranial metastases	0	15	9.36	12	9.69	0.81 (0.18, 3.67)
	1 to 2	45	4.57	57	7.26	0.62 (0.34, 1.12)
	≥3	40	4.24	32	7.33	0.45 (0.22, 0.94)
Presence of liver metastases	Yes	35	3.52	35	6.90	0.43 (0.21, 0.88)
	No	65	6.49	65	8.67	0.64 (0.37, 1.10)
Number of brain metastases	1	9	4.99	22	10.48	0.36 (0.11, 1.19)
	2 to 3	16	10.81	22	Not est	0.65 (0.22, 1.93)
	>3	73	4.39	57	7.00	0.54 (0.32, 0.92)
Sum of Bidimensional products of lesions	<250 mm^2	13	2.66	28	13.21	0.18 (0.06, 0.54)
	250-1000 mm^2	53	6.11	48	5.03	0.98 (0.55, 1.76)
	>1000 mm^2	33	4.27	23	10.51	0.40 (0.17, 0.95)
Timing of Diagnosis	metachronous	96	4.47	97	8.67	0.54 (0.35, 0.84)
	synchronous	4	8.84	3	7.85	0.62 (0.06, 7.00)
Prior treatment for brain metastases	Yes	7	8.05	3	5.75	2.06 (0.29, 14.83)
	No	93	4.47	97	9.00	0.52 (0.33, 0.80)
Mental status	abnormal	7	3.06	15	7.03	0.27 (0.06, 1.25)
	Normal	93	4.99	85	9.69	0.53 (0.34, 0.85)
Baseline hemoglobin	<12 g/dL	27	4.30	22	8.67	0.35 (0.14, 0.85)
	≥12 g/dL	73	5.03	78	9.69	0.61 (0.37, 1.01)
Site location	USA	55	5.85	60	8.67	0.51 (0.29, 0.91)
	Canada	20	4.01	15	9.69	0.39 (0.14, 1.10)
	ROW	25	4.39	25	5.03	0.75 (0.30, 1.86)
Altitude at treatment site	<2000 ft	89	4.99	92	8.67	0.58 (0.37, 0.90)
	≥2000 ft	11	3.48	8	25.72	0.36 (0.07, 1.91)
Weight per dosing adjustment algorithm	High weight	35	8.31	53	9.69	0.65 (0.34, 1.26)
	Low weight	62	4.27	47	7.15	0.49 (0.27, 0.89)

Subsequent therapy is a known factor influencing the survival outcome in studies including patients with primary breast cancer. Importantly, both the Control and RSR13 arms were balanced for types of subsequent treatments (Table 3.15).

Table 3.15
Subsequent Therapies in Patients with Breast Cancer Primary in Study RT-009

Type of Therapy	Control N = 55	RSR13 N = 60
Any systemic n	36	41
Any systemic %	65%	68%
Median time to therapy (months)	0.7	1.0
Brain surgery n	1	1
Brain surgery %	2%	2%
Median time to therapy (months)	3.1	22.0
SRS for brain n	4	3
SRS for brain %	7%	5%
Median time to therapy (months)	4.8	5.6

Comparable survival benefits in favor of RSR13 were seen for the 6 highest enrolling study sites, which enrolled 43% of the breast cancer patients (HR = 0.46; 95% CI: 0.23, 0.93) and the remaining 34 study sites (HR = 0.63; 95% CI: 0.36, 1.11) (Table 3.16). Notably, the survival benefit for the 6 highest enrolling sites was statistically significant and the benefit for the remaining sites neared significance.

Table 3.16
Survival by Investigator Site for Breast Cancer Patients in Study RT-009

Site No.	Number of Deaths/ Number of Patients		Survival Hazard Ratio (95% CI)
	Control	RSR13	
Top 6 sites	22 / 26 (85%)	14 / 24 (58%)	0.462 (0.23, 0.93)
Remaining 34 sites	25 / 29 (86%)	25 / 36 (69%)	0.633 (0.36, 1.11)
All Sites	47 / 55 (86%)	39 / 60 (65%)	0.552 (0.36, 0.85)

To formally test for a differing effect between NSCLC patients and breast primary patients in the eligible NSCLC/breast co-primary population, an interaction test was performed. The results of this partial likelihood ratio test show that the effect in the breast primary patients is substantially larger than in the NSCLC patients ($\chi^2 = 8.46$, $p = 0.01$). This statistical result implies that the population of breast cancer patients should be considered on their own. Although we recognize that the sample size of this population represents 21% (115/538) of the entire RT-009 study population, we believe the highly significant survival benefit achieved in patients with primary breast cancer deems these results relevant for analysis.

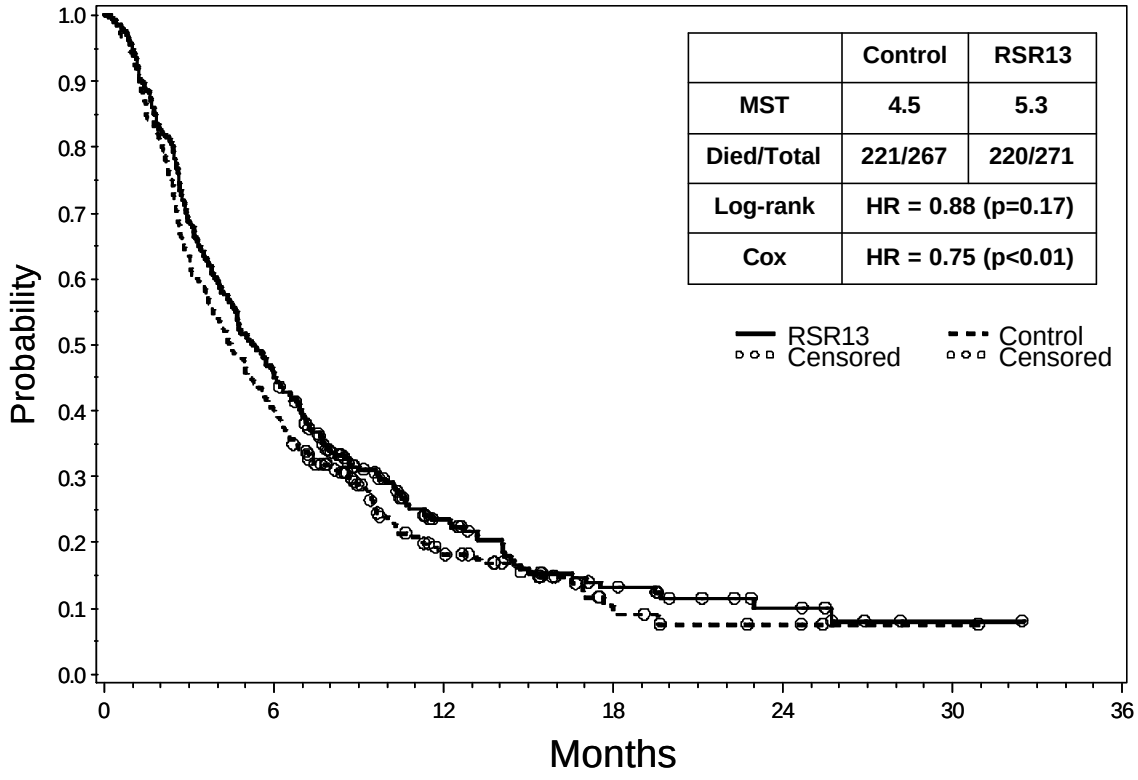
3.2.3.2.4 Survival in Additional Subpopulations

3.2.3.2.4.1 Survival in All Randomized Patients

Per ICH guidelines, analysis for all patients randomized was also performed. However, due to the large discrepancy in survival times for the ineligible patients between treatment arms (MST Control arm vs RSR13 arm: 5.9 vs 3.3 months, respectively), the treatment effect estimates for all randomized patients may not be appropriate. The observed MST for the Control

arm (N = 267) was 4.5 months compared to 5.3 months for the RSR13 arm (N = 271) (Figure 3.5). This treatment effect translated into a hazard ratio of 0.88 via the unadjusted log-rank test (p = 0.17) and a hazard ratio of 0.75 via the prespecified Cox multiple regression model utilizing all covariates simultaneously (p <0.01).

Figure 3.5
Kaplan-Meier Survival Curve for All Randomized Patients
RSR13 Arm (N = 271) versus Control Arm (N = 267)



Of the 17 prespecified covariates that were analyzed for imbalances in study RT-009 between the Control and RSR13 arms, there were 7 covariates that predicted outcome and they are summarized in Table 3.17. There were no covariate imbalances that favored the RSR13 arm. The following covariates favored the Control arm: KPS, prior treatment for brain metastases, number of extracranial metastases, and to a lesser degree, age.

Table 3.17
Seven Covariates Most Predictive of Survival by Treatment Group in Study RT-009, All Randomized Patients

Covariate	Level	Control (N = 267) N (%)	RSR13 (N = 271) N (%)	Predictive Effect (on Survival)	
				HR	p-value[a]
Baseline KPS	**100** **90** **80** **≤70**	43 (16) 100 (37) 80 (30) 44 (16)	34 (13) 124 (46) 64 (24) 49 (18)	≤70 vs 80 vs 90 vs 100	
				0.72	<0.0001
Prior Treatment for Brain Mets	**Yes** **No**	29 (11) 238 (89)	21 (8) 250 (92)	No vs Yes	
				0.44	<0.0001
N. of Extra-cranial Mets	**0** **1-2** **>2**	96 (36) 124 (46) 47 (18)	84 (31) 128 (47) 59 (22)	0 vs 1-2 vs >2	
				1.42	0.0001
Gender	**Female** **Male**	150 (56) 117 (44)	153 (56) 118 (44)	Female vs Male	
				1.43	0.002
Breast Primary	**Yes** **No**	55 (21) 212 (79)	60 (22) 211 (78)	No vs Yes	
				0.61	0.003
Age Group	**<65** **³65**	197 (74) 70 (26)	196 (72) 75 (28)	<65 vs ≥65	
				1.41	0.004
Log (Baseline Hgb)	**Mean** **SD**	2.599 0.116	2.588 0.112	Log (Hgb) vs Log (Hgb) + 1	

[a]p-values represent the mean of p-values from the 48 Cox models; the covariates were statistically significant in all 48 models.

Beginning with a Cox model that included only treatment arm, Table 3.18 shows how adding covariates one-at-a-time, based on their statistical significance in the full Cox model, affects the RSR13 treatment effect estimate. After adjusting for KPS, prior brain tumor resection, and presence of extracranial metastases, the 3 most significant covariates in the full Cox model, the RSR13 treatment effect has a p-value of 0.03.

Table 3.18
RSR13 Treatment Effect Correcting for Imbalances[a]

Covariates in Cox Model	RSR13 Effect
---	HR = 0.88, p = 0.17
KPS	HR = 0.86, p = 0.11
KPS, Prior resection	HR = 0.83, p = 0.05
KPS, Prior resection, Number of Extracranial Metastases	HR = 0.81, p = 0.03
KPS, Prior resection, Number of Extracranial Metastases, Gender	HR = 0.79, p = 0.02
KPS, Prior resection, Number of Extracranial Metastases, Gender, Breast Primary	HR = 0.80, p = 0.02
KPS, Prior resection, Number of Extracranial Metastases, Gender, Breast Primary, Age Group	HR = 0.79, p = 0.02
KPS, Prior resection, Number of Extracranial Metastases, Gender, Breast Primary, Age Group, Baseline Hgb	HR = 0.78, p = 0.01

[a]Last row contains all covariates that were statistically significant (p <0.05)

We conclude then that when adjusted for imbalances in prognostic variables by the use of a Cox model, the results of study RT-009 show a clear and compelling statistically significant difference in survival in favor of the patients that received RSR13 over the Control arm. The survival results are presented by stratum in Table 3.19.

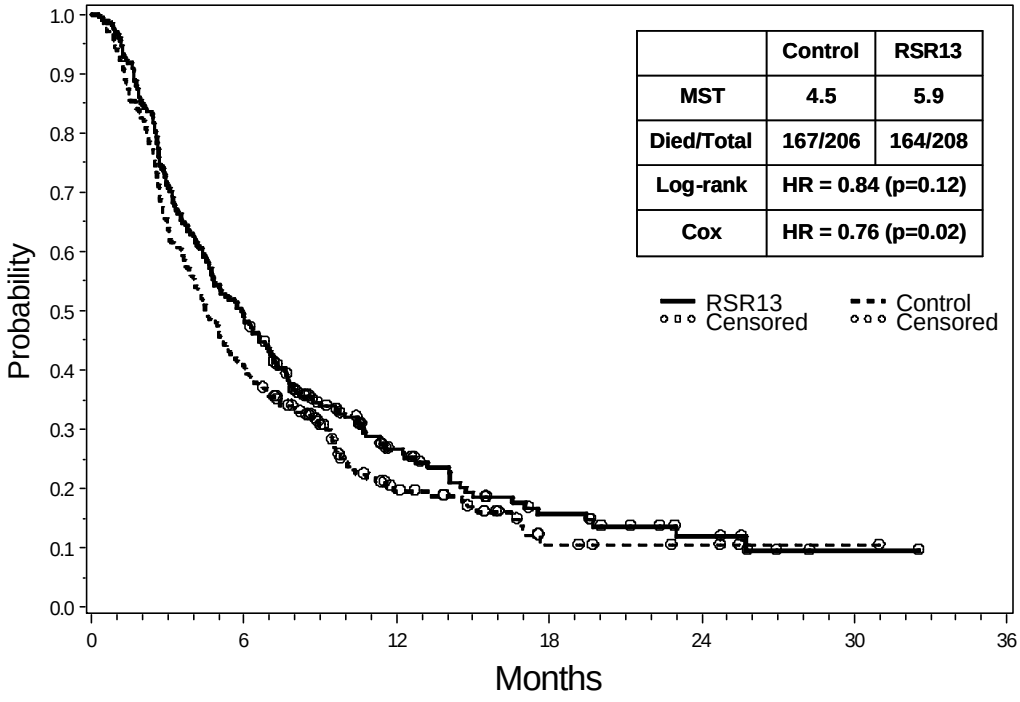
Table 3.19
Survival by Stratum for All Randomized Patients

Stratum	Control (N = 267) MST (months)	RSR13 (N = 271) MST (months)	RSR13 Effect	
			HR (95% CI)	p-value
1	7.0 (n = 24)	4.2 (n = 22)	1.06 (0.54, 2.09)	0.86
2	4.1 (n = 136)	5.3 (n = 133)	0.93 (0.72, 1.21)	0.60
3	4.5 (n = 50)	7.3 (n = 56)	0.54 (0.35, 0.85)	<0.01
4	3.7 (n = 57)	3.9 (n = 60)	1.07 (0.73, 1.57)	0.73

3.2.3.2.4.2 Survival in All Randomized Patients in the NSCLC/breast Population:

The observed MST for the Control arm (N = 206) was 4.5 months compared to 5.9 months for the RSR13 arm (N = 208) (Figure 3.6). This treatment effect translated into a hazard ratio of 0.84 via the unadjusted log-rank test (p = 0.12) and a hazard ratio of 0.76 via the prespecified Cox multiple regression model utilizing all covariates simultaneously (p = 0.02).

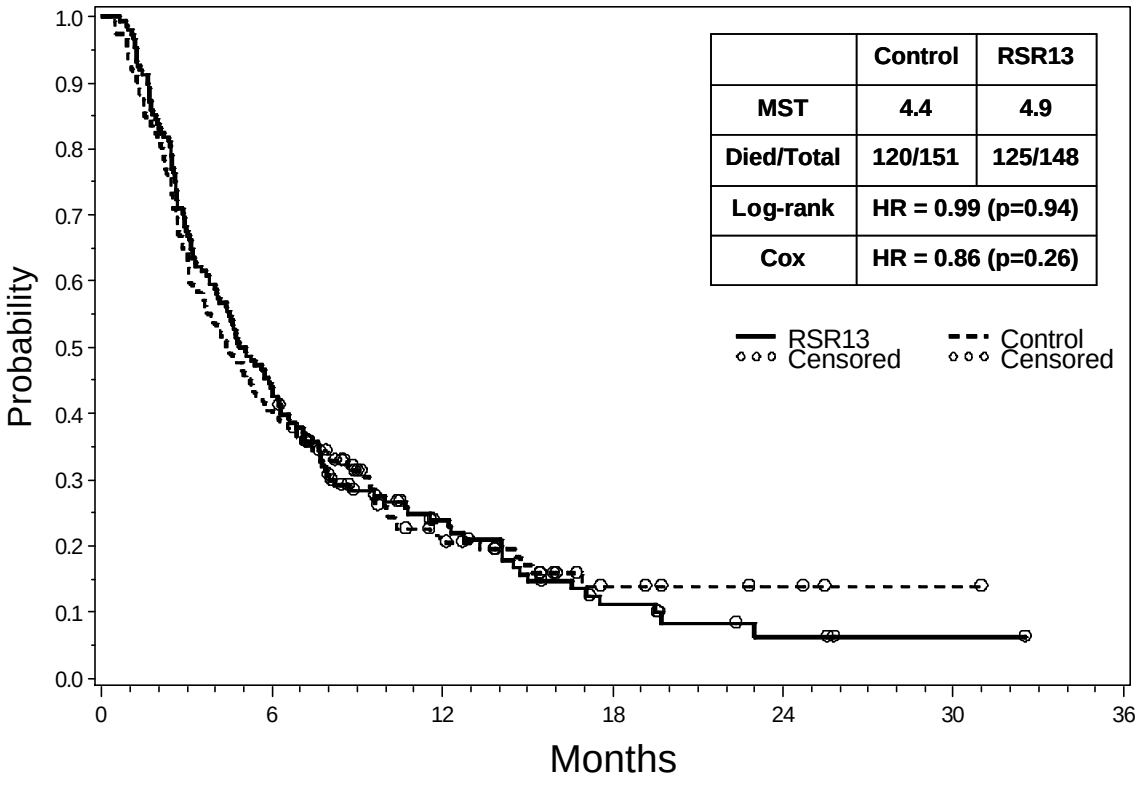
Figure 3.6
Kaplan-Meier Survival Curve for All Randomized NSCLC/breast Patients
RSR13 Arm (N = 208) versus Control Arm (N = 206)



3.2.3.2.4.3 Survival in Patients with NSCLC

The observed MST for the Control arm (N = 151) was 4.4 months compared to 4.9 months for the RSR13 arm (N = 148) (Figure 3.7). This treatment effect translated into a hazard ratio of 0.99 via the unadjusted log-rank test (p = 0.94) and a hazard ratio of 0.86 via the prespecified Cox multiple regression model utilizing all covariates simultaneously (p = 0.26). The reasons for the difference in efficacy results between the NSCLC and breast cancer populations are outlined in Section 3.2.3.5.

Figure 3.7
Kaplan-Meier Survival Curve for All Randomized Patients with NSCLC Primary RSR13 Arm (N = 148) versus Control Arm (N = 151)



3.2.3.3 Secondary Endpoint: Response Rate in the Brain

3.2.3.3.1 Response Rate in the Brain for All Randomized Patients

Best maximal response was determined from magnetic resonance image (MRI) or computed tomography (CT) scans performed at baseline, initial follow-up 1 month after WBRT day 10, 3 months after WBRT day 10, and every 3 months thereafter until progression. A central, independent radiologic review blinded to treatment arm and outcome was conducted for all scans by the Neuroimaging Core Laboratory (Cleveland Clinic). The point estimates of response rate (complete plus partial response) were 37.5% in the Control arm and 45.4% in the RSR13 arm (Table 3.20). The estimated increase in response rate in patients receiving RSR13 was 7.9% with an associated 95% CI of –0.4% to 16.3% (p = 0.06). Furthermore, 10% of patients in the RSR13 arm had a complete response (CR) as best response compared to 6% in the Control arm.

Table 3.20
Survival by Best Response for All Patients in Study RT-009

	Control (N = 267) n (%)		**RSR13 (N = 271) n (%)**	
	N (%)	MST	n (%)	MST
CR	16 (6)	10.02	28 (10)	---
PR	84 (31)	6.57	95 (35)	7.62
SD	83 (31)	4.37	72 (27)	4.21
PD	33 (12)	5.59	34 (13)	5.32
Missing	51 (19)	1.31	42 (15)	1.23

3.2.3.3.2 Response Rate in the Brain for All Randomized Patients in the NSCLC/breast Population

The point estimates of response rate (complete plus partial response) were 40.8% in the Control arm and 52.9% in the RSR13 arm (Table 3.21). The estimated increase in response rate in patients receiving RSR13 was 12.1% with an associated 95% CI of 2.5% to 21.7% (p = 0.01). Furthermore, 13% of patients in the RSR13 arm had a CR as best response compared to 7% in the Control arm.

Table 3.21
Survival by Best Response for NSCLC/Breast Patients in Study RT-009

	Control (N = 206) n (%)		**RSR13 (N = 208) n (%)**	
	n (%)	MST	n (%)	MST
CR	15 (7)	10.02	27 (13)	---
PR	69 (33)	6.28	83 (40)	7.69
SD	64 (31)	4.58	57 (27)	4.37
PD	20 (10)	5.77	15 (7)	5.39
Missing	38 (18)	1.30	26 (13)	1.51

3.2.3.3.3 Response Rate in the Brain for All Patients with Breast Cancer

A total of 102 patients had a scan after treatment from which to assess response; 47 patients in the Control arm and 55 patients in the RSR13 arm (Table 3.22). The point estimates of response rate (complete plus partial response) were 49.1% in the Control arm and 71.7% in the RSR13 arm. The estimated increase in response rate in patients receiving RSR13 was 22.6% with an associated 95% confidence interval of 5.1% to 40.0% (p = 0.01). Furthermore, 13% of patients in the RSR13 arm had a CR as best response compared to 9% in the Control arm. For patients in Stratum 3, the estimated increase in response rate in patients receiving RSR13 was 21.6% with an associated 95% confidence interval of 3.3% to 40.0%.

Table 3.22
Survival by Best Response for Patients with Breast Cancer Primary in Study RT-009

	Control (N = 55)		RSR13 (N = 60)	
	n (%)	MST	n (%)	MST
CR	5 (9)	8.94	8 (13)	---
PR	22 (40)	5.62	35 (58)	10.48
SD	15 (27)	3.84	12 (20)	3.96
PD	5 (9)	4.99	0	---
Missing	8 (15)	2.87	5 (8)	0.99

3.2.3.3.4 Confirmed Response Rate

Confirmation of response was not required per protocol; however, many patients had additional follow-up scans a minimum of 4 weeks after the initial determination of response. An additional analysis was conducted to support this endpoint. Confirmed responses were those responses that were identified as either CR or partial response (PR) on 2 consecutive scans at least 4 weeks apart. The results of this analysis show a statistically significant improvement in confirmed response rate (CR+PR) for patients in the RSR13 arm compared to patients in the Control arm for both co-primary populations as well as for breast cancer patients (Table 3.23).

Table 3.23
Confirmed Response Rate (CR+PR)

	Control	RSR13	p-value
All Randomized Patients	17%	25%	0.02
NSCLC/breast Patients	20%	29%	0.03
Breast Cancer Patients	21%	41%	<0.01

3.2.3.4 Other Secondary Endpoints

Tables 3.24, 3.25, and 3.26 summarize the differences in secondary endpoints between RSR13 and Control arms for all randomized patients (N = 538), for all randomized NSCLC/breast patients (N = 414), and all randomized patients with breast cancer primary (N = 115), respectively.

Table 3.24
Differences between RSR13 and Control Arms by Endpoint for All Randomized Patients (N = 538)

Endpoint	Control (N = 267)	RSR13 (N = 271)	p-value
QOL			
KPS (% stable/improving at 3 months)	18%	24%	<0.01[a]
Spitzer Questionnaire (% stable/improving at 3 months)	21%	23%	0.06[a]
Cause of Death (% Neurologic)[b]	15	17	0.51
Time to clinical progression (% PF at 3 months)	64	72	0.44
Time to radiographic progression (% PF at 3 months)	85	84	0.50

PF = progression-free
[a]Cochran-Mantel-Haenszel test with time (1, 3, 6, and 12 months) as strata
[b]Percent of all patients that died

Table 3.25
Differences between RSR13 and Control Arms by Endpoint for All Randomized NSCLC/breast Patients (N = 414)

Endpoint	Control (N = 206)	RSR13 (N = 208)	p-value
QOL			
KPS (% stable/improving at 3 months)	19	26	<0.01[a]
Spitzer Questionnaire (% stable/improving at 3 months)	22	26	0.01[a]
Cause of Death (% Neurologic)[b]	16	18	0.38
Time to clinical progression (% PF at 3 months)	65	75	0.21
Time to radiographic progression (% PF at 3 months)	89	90	0.88

PF = progression-free
[a]Cochran-Mantel-Haenszel test with time (1, 3, 6, and 12 months) as strata
[b]Percent of all patients that died

Table 3.26
Differences between RSR13 and Control Arms by Endpoint for All Randomized Patients with Breast Cancer Primary (N = 115)

Endpoint	Control (N = 55)	RSR13 (N = 60)	p-value
QOL			
KPS (% stable/improving at 3 months)	18	35	<0.01[a]
Spitzer Questionnaire (% stable/improving at 3 months)	24	37	0.01[a]
Cause of Death (% Neurologic) [b]	17	21	0.23
Time to clinical progression (% PF at 3 months)	86	91	0.36
Time to radiographic progression (% PF at 3 months)	90	98	0.80

PF = progression-free
[a]Cochran-Mantel-Haenszel test with time (1, 3, 6, and 12 months) as strata
[b]Percent of all patients that died

The treatment effect of RSR13 in several of the secondary endpoints was inconclusive. For time to radiographic progression and time to clinical progression, too much censoring resulted in low power. Images were only assessed every 3 months. Therefore, most patients that died did not have an opportunity to have a brain scan to detect progression (or lack thereof) in the brain. Due to the low number of events for this endpoint, the statistical test was inconclusive. In addition, there were too many competing risks (eg, systemic death) to accurately determine time to radiographic and clinical progression. Cause of death was difficult to accurately determi ne and there was a high variability in assessment between sites.

3.2.3.5 Differences between NSCLC and Breast Patients

The reasons why RSR13 as an adjunct to WBRT had a larger treatment effect in patients with breast cancer and brain metastases are many and may include the following: radiobiology, growth fraction, and effect of subsequent therapy. However, the principle reason why RSR13 had a larger treatment effect in breast cancer patients was likely due to differences in dosing between NSCLC and breast cancer patients. PK studies have revealed that patients with breast cancer were more effectively dosed than patients with NSCLC and this is discussed in Section 3.2.3.5.1.

3.2.3.5.1 Differences in Dosing

A critical determinant of RSR13 PK and RSR13 exposure is the patient's body weight category. The volume of distribution for RSR13 is the intravascular compartment, but RSR13 is dosed based on actual body weight, which does not correlate well with intravascular volume. For example, a lean 60 kg patient may have a volume of distribution roughly equal to a 90 kg patient who has a higher percentage of body fat. If both patients receive a 100 mg/kg dose of RSR13, there will be a higher concentration of RSR13 in RBCs in the 90 kg patient versus the 60 kg patient.

In order to completely determine the impact of dosing throughout the course of the treatment in study RT-009, it is important to summarize Amendment 2 of the study protocol (Protocol Version 3), which was implemented 05 Jun 2001. According to Amendment 2 the following patients would receive a lower starting dose of RSR13 (75 mg/kg instead of 100 mg/kg):

- Patients receiving anti-hypertensives
- Patients with a prior nephrectomy
- HW females (body weight over 70 kg)
- HW males (body weight over 95 kg)

The intent of Amendment 2 (Protocol Version 3) was to decrease the starting dose of RSR13 in HW patients to reduce the likelihood of terminations. Prior to this amendment, there was already a higher percentage of patients with dose adjustments in study than in study RT-008 (Table 3.27). After this amendment, there was an increase in the percentage of study RT-009 patients receiving RSR13 who had a starting dose at a reduced dose level, both in patients with NSCLC and in breast cancer patients, compared to Protocol Versions 1 and 2. Half of the patients with breast cancer and 41% of the patients with NSCLC received a starting dose of RSR13 of 75 mg/kg, instead of 100 mg/kg, which compares to 4% and 16% before Protocol Version 3.

Table 3.27
Percentage of Patients who Received Dose Adjustments in Studies RT-008 and RT-009

Primary Site	Study		
	RT-008 %	**RT-009 Versions 1,2 %**	**RT-009 Versions 3,4 %**
NSCLC	N = 39	N = 61	N = 87
Initial Dose <100 mg/kg	8	16	41
Drug Terminated	13	20	16
Doses Held	15	27	43
Doses Reduced	31	45	52
Breast Cancer	N = 21	N = 26	N = 34
Initial Dose <100 mg/kg	0	4	50
Drug Terminated	33	31	15
Doses Held	24	38	36
Doses Reduced	33	62	48

As stated above, body weight category is a critical determinant of RSR13 PK and RSR13 exposure, and therefore, differences in weight across populations are likely to influence outcome. Using the weight cut-off specified in Amendment 2 of study RT-009, Table 3.28 shows the frequency of HW and LW patients across primary tumor type for both genders. The percentage of LW patients is much lower in patients with breast cancer primary than in patients with NSCLC primary (47% vs 83%, respectively). Furthermore, the mean weight of female patients with NSCLC primary was lower than the mean weight of female patients with breast cancer primary (57.4 vs 61.3 kg, respectively).

Table 3.28
Body Weight in Study RT-009 by Body Weight Category, Gender, and Primary Site

Primary Site and Gender	Weight					
	Low			High		
	Number of Samples	%	Mean (kg)	Number of Samples	%	Mean (kg)
NSCLC						
Male	71	89	72.6	9	11	105.8
Female	52	76	57.4	16	24	81.2
Total	123	83	66.2	25	17	90.0
Breast						
Female	28	47	61.3	32	53	83.6

As detailed in Table 3.29, LW patients had lower RSR13 RBC compared with HW patients. Furthermore, the mean RSR13 RBC concentration determined in LW NSCLC patients receiving 75 mg/kg is 430 µg/ml. This concentration would be expected to result in a suboptimal p50 shift, according to data detailed in Section 2.0. A similar dose of RSR13 in LW breast cancer patients resulted in a mean RSR13 concentration in RBCs of 493 µg/ml. This concentration would be sufficient to consistently produce a p50 shift near the desired 10 mmHg.

Table 3.29
RSR13 RBC Concentrations (µg/mL) in Study RT-009, by Weight Category and Primary Site

Primary Site and Dose (mg/kg)	Low Body Weight		High Body Weight	
	Number of Samples	Median Concentration	Number of Samples	Median Concentration
NSCLC				
75	58	430	14	554
100	108	556	22	736
Breast				
75	13	493	16	505
100	24	635	26	708

Further evidence that LW NSCLC patients were dosed ineffectively is evident if results are analyzed by weight group (Table 3.30). This shows a clear treatment effect in HW NSCLC patients (HR = 0.75 vs 1.06 [neutral], respectively).

Table 3.30
RSR13 Treatment Effect by Weight Group for NSCLC Patients in Study RT-009

Weight Group	Response Rate Improvement (95% CI)	Survival HR (95% CI)
Low Body Weight	7% (-6%, 19%)	1.06 (0.79, 1.40)
High Body Weight	12% (-14%, 38%)	0.75 (0.42, 1.35)

When the results in NSCLC patients are adjusted by dosing and PK (Table 3.31), it is evident that if RSR13 doses are administered effectively, NSCLC patients can derive benefit from RSR13. NSCLC patients with ≥7 doses of RSR13 and with ≥7 successful doses (a successful dose is one that results in an RSR13 concentration in RBCs of at least 483 mg/mL) had a greater response rate and twice as many NSCLC patients with a best response of CR versus Control patients who received ≥7 doses. In addition, for patients with ≥7 doses of RSR13 and with ≥7 successful doses, 57% of NSCLC patients were responders. However, 43% of NSCLC patients with ≥7 doses of RSR13 but with <7 successful doses were responders and 30% of NSCLC patients with <7 doses of RSR13 were responders. It is important to note that the NSCLC patients with ≥7 doses of RSR13 but with <7 successful doses received the same amount of drug as the NSCLC patients with ≥7 doses of RSR13 and with ≥7 successful doses, but the latter had higher (ie, successful) RSR13 RBC concentrations than the former and there is a clear difference in response rate between the 2 groups.

Table 3.31
Response Rate by Exposure Group for NSCLC Patients in Study RT-009

Best Response	Control <7 Doses WBRT (N = 4) %	Control ³7 Doses WBRT (N = 147) %	RSR13 <7 Doses (N = 30) %	RSR13 ³7 Doses <7 Doses Successful (N = 65) %	RSR13 ³7 Doses ³7 Doses Successful (N = 53) %
CR	0	7	10	12	15
PR	0	32	20	31	42
SD	0	33	23	35	28
PD	0	10	3	11	13
Unknown	100	18	43	11	2

3.2.3.5.2 Dosing Conclusions

- Dose adjustments from 100 mg/kg to 75 mg/kg have a greater impact on LW patients
- A higher percentage of the NSCLC patients were LW compared with the breast cancer patients
- Based on the PK results we conclude that the LW patients with NSCLC were underdosed, and when the results in NSCLC patients are analyzed taking into account drug exposure there is a clear RSR13 treatment effect in NSCLC patients

3.2.3.6 Efficacy Conclusions

The results of study RT-009 confirm the hypothesis that RSR13 enhances the efficacy of WBRT in patients with brain metastases. Study RT-009 showed an improvement in survival in 1 of the 2 co-primary populations (Eligible NSCLC/breast cancer patients). This result reached statistical significance with additional follow up and it is supported by the fact that RSR13 produced a statistically significant improvement in the response rate in the brain in this population. In addition, when the results of study RT-009 are analyzed by the prespecified Cox multiple regression model, the results of the study in both prespecified co-primary populations show a 24% reduction in the risk of death due to RSR13.

The results of study RT-009 are driven by the large treatment effect in the breast cancer population. In these patients we observed a clinically meaningful prolongation in survival due to RSR13. This improvement in survival is supported by the significant increase in response rate in the brain produced by the addition of RSR13. Improved QOL measures were also observed in the breast cancer patients that received RSR13.

4.0 SUPPORTIVE PHASE 2 STUDY FOR THE TREATMENT OF PATIENTS WITH BRAIN METASTASES (RSR13 RT-008)

4.1 Study Design

RT-008 was a non-randomized, open-label, multi-center, efficacy, safety, and PK/PD study of patients receiving RSR13 as adjunct to a conventional 2-week course of WBRT for brain metastases. Planned enrollment was 104 patients, 54 with RTOG RPA of prognostic factors criteria for Class I and 50 with RTOG RPA Class II brain metastases. The objectives of RT-008 were to evaluate overall MST (primary endpoint), response rate (CR and PR in the brain), and time to tumor progression in the brain in patients after receiving daily IV doses of 100 mg/kg RSR13 administered over 30 minutes with standard WBRT for brain metastases. Patients received WBRT, 30 Gy in 10 fractions of 3.0 Gy each, preceded by RSR13, 50-100 mg/kg IV over 30 minutes via a CVAD. Patients also received supplemental oxygen at 4 L/minute via nasal cannula for at least 5 minutes before the start of RSR13 administration. Oxygen was administered continuously during each RSR13 infusion and WBRT treatment until the patient's SpO_2 on room air was stable at ≥90%.

Survival data were analyzed using unadjusted log-rank test, Kaplan-Meier estimates, and a multivariable Cox proportional hazards regression model with baseline characteristics and study group as factors. In a separate protocol-specified analysis, survival results from the Class II patients in this study were compared to the RTOG BMD. In addition, a comparison of survival data (with a stratified Cox model) was also conducted for Class II patients who were case-matched exactly (exact-matched controls) by KPS, primary tumor site, status of extracranial metastases, status of primary tumor, and age (within 5 years) to patients from the RTOG BMD.

4.2 Demography and Baseline Characteristics of Patients with Brain Metastases in RT-008

Patients were enrolled from 17 investigational sites during the period from 24 Feb 1998 to 28 May 1999. Actual enrollment/analysis included 12 Class I and 57 Class II patients. Study enrollment was closed shortly after the Class II enrollment target was met; at that time only 12 Class I patients had been enrolled. A total of 12 RPA Class I patients, 33 RPA Class II patients with NSCLC primary, 18 RPA Class II patients with breast cancer primary, and 6 RPA Class II patients with other types of primary were enrolled. Demographics are presented in Table 4.1.

Table 4.1
Summary of Demographic Data in Control and RSR13 Treated Patients in RT-008

Parameter	RT-008 RSR13 (N = 69)
Sex n (%)	
Male	31 (45)
Female	38 (55)
Race n (%)	
Caucasian	62 (90)
Black	5 (7)
Native American	0 (0)
Asian	0 (0)
Hispanic	2 (3)
Other	0 (0)
Age (years)	
<65 years n (%)	51 (74)
≥65 years n (%)	18 (26)
Mean	55.8
SD	10.4
Min-Max	37-76
Weight (kg)	
Mean	73.0
SD	14.5
Min-Max	38.6-129.1
n Missing	0
RPA Classification n (%)	
RPA Class I	12 (17)
RPA Class II – NSCLC primary	33 (48)
RPA Class II – Breast cancer primary	18 (26)
RPA Class II – Other primary tumor type	6 (9)
Screening Resting SpO_2[a]	
<96%	17 (25)
≥96%	52 (75)

[a]Missing baseline resting SpO_2 counted in the <96% category.

The median duration of primary disease was similar for Class I and Class patients; however, Class II patients with primary breast cancer had a longer median duration of primary disease than patients with other types of primary disease (Table 4.2). The duration of NSCLC was shorter than other types of primary disease (particularly in Class II patients) due to the fact that most patients with NSCLC had synchronous metastases. The median duration of primary disease in RPA Class II patients with breast cancer primary was similar between studies RT-008 and RT-009 (43.0 vs 43.4 months, respectively).

Table 4.2
Tumor History by RPA Class for RSR13 Treated Patients in RT-008

RPA Class	Primary Disease	n	Median Age (years)	Controlled Primary No/Yes	Median Duration of Primary Disease (months)	Extra-cranial Mets No/Yes[a]	Median Duration of Brain Mets (months)	Median Baseline KPS
I	NSCLC	6	56.5	0/6	11.5	6/0	0.2	90
	Breast	3	42.0	0/3	12.8	3/0	0.1	90
	Other	3	53.0	0/3	14.3	3/0	0.4	90
	Total	12	52.5	0/12	12.3	12/0	0.2	90
II	NSCLC	33	61.0	26/7	0.8	14/19	0.4	90
	Breast	18	49.5	8/10	43.0	0/18	0.2	90
	Other	6	61.0	4/2	27.2	1/5	0.7	80
	Total	57	56.0	38/19	12.4	15/42	0.3	90
All		69	55.0	38/31	12.3	27/42	0.3	90

[a]Extracranial metastases were not documented in Class I patients (per definition).

4.3 Dosing

The original study protocol specified an RSR13 dose of 100 mg/kg, however the protocol was later amended (Amendment 3) to allow for RSR13 dose reductions to 75 or 50 mg/kg (or withholding of doses) if clinical assessments or laboratory criteria indicated that the patient was experiencing exaggerated pharmacological effects. However, as presented in Table 3.27, there were fewer dose reductions in study RT-008 than in study RT-009.

4.4 Efficacy Results

The observed Kaplan-Meier estimate of MST for the overall RSR13-treated population was 6.4 months and the MST for the Class I and II groups was also 6.4 months for each group. After 6 months of follow-up, 51% (35/69) of all RT-008 patients were alive and 33% (23/69) were alive and free of intracranial progression. Extracranial progression was experienced by 61% (42/69) of all patients by the end of the follow-up period (>24 months).

KPS measurements demonstrated that approximately 6 months after the start of treatment the majority of living patients had an acceptable performance status. At the 5-7 month period 70% (16/23) of living patients with KPS scores available had little or no change from baseline in their KPS score. MMSE measurements demonstrated that approximately 6 months after the start of treatment the mental state of the majority of living patients was stable or improved from baseline.

Patients with a CR or PR survived longer and remained free of intracranial progression for a longer time than patients with a response of SD. In addition, patients with a CR or PR were more likely to have maintained their neurological function status from baseline to follow-up than patients with a response of SD or Other.

Patients in the RT-008 Class II group (n = 57) had statistically significantly improved survival compared to the RTOG BMD (n = 1070; p = 0.017). The observed Kaplan-Meier MST for the Class II group was 6.4 months (95% CI: 4.4-9.0 months), compared to 4.1 months (CI: 3.8-4.5 months) for the RTOG BMD control group (Table 4.3). Based on a Cox multiple-regression model analysis, the risk of death was reduced by 22% for patients in the Class II group versus patients in the RTOG BMD (p = 0.098).

Table 4.3
Survival Data
RTOG Brain Metastases Database Class II Patients versus RSR13 Class II Patients

	All Patients			
	RTOG BMD Class II		RSR13 Class II	
Time (Months)	**% Alive**	**No. at Risk**	**% Alive**	**No. at Risk**
0	100	1070	100	57
6	35	376	51	29
12	15	157	23	13
18	6	66	12	7
24	3	30	11	6
Median	4.1 months		6.4 months	
Dead/Total	1049/1070		54/57	
p-value	0.017			
95% CI	[3.8-4.5 months]		[4.4-9.0 months]	

A subset of Class II patients (n = 38) in the study could be case-matched exactly by KPS, primary tumor site, extent of metastases, status of primary tumor, and age (within 5 years) to patients from the RTOG BMD (n = 38). As shown in Table 4.4, using exact case-matched RTOG BMD controls, the difference in survival was even more significant (p = 0.0060) than in the overall comparison, with MST at 7.3 months (CI: 4.6-10.9 months) versus 3.4 months (CI: 1.7-5.0 months).

Table 4.4
Survival Data
RTOG Brain Metastases Database (Exact Matches) versus RSR13 Class II Patients

	All Patients			
	RTOG BMD Class II		RSR13 Class II	
Time (Months)	**% Alive**	**No. at Risk**	**% Alive**	**No. at Risk**
0	100	38	100	38
6	21	8	58	22
12	8	3	24	9
18	3	1	13	5
24	3	1	13	5
Median	3.4 months		7.3 months	
Dead/Total	38/38		36/38	
p-value	0.0060			
95% CI	[1.7-5.0 months]		[4.6-10.9 months]	

A stratified Cox model, with each case-matched pair (RTOG BMD:RSR13) as a stratum, and study group as the only independent factor was also used to estimate RSR13 treatment effect. For the case-matched controls (n = 38), there was a 54% reduction in the risk of death for patients who received RSR13/RT versus RTOG BMD patients (p = 0.0267).

4.5 Comparison of Results from Studies RT-008 and RT-009

Table 4.5 demonstrates that the efficacy results are consistent between studies RT-008 and RT-009 and add further support to the validity of the treatment effect in study RT-009 patients with breast cancer primary.

Table 4.5
Survival in RPA Class II Breast Cancer Patients, Studies RT-008 and RT-009

Study and Analysis	Control MST (months)	RSR13 MST (months)	p-value
RT-008	5.4 (n = 113)	9.7 (n = 18)	0.54
RT-008: RTOG Case Matching	4.9 (n = 12)	7.9 (n = 12)	0.03
RT-009 Stratum 3	4.5 (n = 49)	7.0 (n = 52)	0.01

5.0 SAFETY

5.1 Studies Evaluated for Safety of RSR13 as an Adjunct to WBRT in Patients with Brain Metastases from Breast Cancer

Development of the RSR13 safety profile specific to the indication of WBRT for brain metastases from breast cancer is based upon data obtained in 7 Phase 1-3, radiation oncology studies that employed multiple-dose regimens of RSR13 as sole adjunct to RT. The 7 studies are RT-002, RT-006, RT-007, RT-007b, RT-008, RT-009, and RT-010.

Data obtained in the controlled Phase 3 study, RT-009, and that of the Phase 2 study, RT-008, provided the pivotal evaluation of the RSR13 safety profile in the target population of patients with brain metastases.

5.2 Extent of Exposure

5.2.1 RSR13 Exposure

A total of 535 patients have received at least 1 dose of RSR13 as sole adjunct to RT. Table 5.1 summarizes the overall exposure for patients in the safety population, which was comprised of patients from the 7 oncology studies that employed multiple dose regimens of RSR13 as sole adjunct to RT. A total of 547 patients were enrolled in these studies, 538 patients were assigned to the RSR13 arm, and 535 patients received at least 1 dose of RSR13. Various RT regimens were utilized across all multiple dose RT studies. The number of RT and RSR13 doses varied substantially between studies (10-32 treatments); therefore, exposure to RSR13 as part of a 10-day treatment regimen with standard WBRT for the treatment of brain metastases in the proposed indication is presented separately. The exposure to RSR13 varied across RT studies with a mean number of daily doses ranging from 5.8-26.8 and the mean daily dose ranging from 77.7-98.3 mg/kg. The duration of infusion was approximately 60 minutes in 2 studies (RT-002 and RT-006) and approximately 30 minutes in all other studies. A total of 80 patients with brain metastases originating from breast cancer have received at least 1 dose of RSR13 (studies RT-009 and RT-008).

Table 5.1
Extent of RSR13 Exposure for All Patients Undergoing RT
for Treatment of Solid Tumors of Different Types, Multiple Dose RSR13 Radiation Oncology Studies

		All RSR13 (Total = 547)[a]
Number of RSR13 Doses	n [b]	535
	Mean	13.9
	SD	2.6
	Min-Max	1-34
RSR13 Dose (mg/kg)	n [b]	535
	Mean	88.6
	SD	13.6
	Min-Max	1.9-106.7
RSR13 Duration (min)	n [b]	534
	Mean	33.2
	SD	8.6
	Min-Max	3.0-83.0

[a]Total: This denominator includes patients undergoing WBRT for brain metastases in studies RT-008 and RT-009, in addition to treated patients in RT-002, RT-006, RT-007/7b, and RT-010.
[b]n: Total number of patients treated with RSR13 (ie, received at least 1 dose RSR13)

When analyzing only patients in studies RT-008 and RT-009, the overall exposure to RSR13 in patients undergoing WBRT for treatment of brain metastases demonstrated the consistency of treatment in this patient population. The mean numbers of daily doses were 8.9 in study RT-008 and 8.4 in study RT-009; the mean daily dose was 92.8 and 84.5 mg/kg, respectively. The decrease in the daily RSR13 dose of study RT-009 compared to study RT-008 was due was due to implementation of dosing adjustment guidelines in study RT-009. These guidelines were expanded in Amendment 2 of the protocol to calculate starting dose and subsequent dosing adjustments according to body weight and gender to decrease the frequency and severity of treatment-emergent adverse events in females and patients with high body weight.

The overall exposure of RSR13 in patients with brain metastases from breast cancer was consistent across study RT-008 and the RSR13 arm of studynRT-009 (Table 5.2). The mean number of doses in patients with brain metastases from breast cancer was 8 in both studies, and the mean daily dose was 93.1 mg/kg in study RT-008 and 84.7 mg/kg in the RSR13 arm of study RT-009.

Table 5.2
Extent of RSR13 Exposure in Patients with Primary Breast Cancer Undergoing WBRT for Treatment of Brain Metastases (Studies RT-008 and RT-009)

		RT-008 (Breast)	RT-009 (Breast RSR13 arm)	All RSR13 [a] (Breast)
Number of RSR13 Doses	n[b]	21	59[c]	80
	Mean	8.0	8.0	8.0
	SD	2.4	3.0	2.8
	Min-Max	2/10	1/10	1/10
RSR13 Dose (mg/kg)	n[b]	21	59[c]	80
	Mean	93.1	84.7	86.9
	SD	12.1	12.9	13.2
	Min-Max	61.8/100.3	50/101.3	50/101.3
RSR13 Duration (min)	n[b]	21	59[c]	80
	Mean	30.3	31.4	31.1
	SD	0.8	3.5	3.1
	Min-Max	29.7/52.8	27.6/47.9	27.6/47.9

Mean: arithmetic mean
SD: standard deviation
Min-Max: minimum-maximum amount
[a]All RSR13 includes all patients with primary breast cancer in studies RT-008 and RT-009.
[b]n: Total number of patients treated with RSR13 (ie, received at least 1 dose RSR13)
[c]Of the 60 patients with primary breast cancer enrolled in the RSR13 arm, 1 patient did not receive RSR13.

5.2.2 RT Exposure

RSR13 as an adjunct to WBRT did not adversely affect the delivery of planned RT. When patients that received RT alone were compared to patients who received RT with RSR13 in studies RT-008 and RT-009, there was no difference in the mean number of RT doses administered (9.9 [SD = 0.6] vs 9.6 [SD = 1.6], respectively) or in the mean total RT dose administered (29.6 Gy [SD = 2.0] vs 29.3 Gy [SD = 3.4], respectively).

5.3 Safety in the Pivotal Phase 3 Efficacy Study, RT-009

5.4 Summary of Adverse Events

Overall, 95.8% (252/263) of the patients in the Control arm and 98.1% (261/266) of the patients in the RSR13 arm experienced at least 1 treatment-emergent adverse event. While the overall incidences of treatment-emergent adverse events were comparable in the 2 treatment arms, the most commonly reported treatment-emergent adverse events in the RSR13 arm were headache and nausea, both reported in 45% (120/266) of RSR13-treated patients, and the most frequently reported treatment-emergent adverse event in the Control arm was fatigue reported in 39% (102/263) of Control patients.

The overall occurrence of Grade 3 or 4 adverse events in RSR13-treated patients was essentially equivalent to that observed in Control patients. However, the most commonly reported Grade 3 adverse event in RSR13-treated patients was hypoxemia, reported in 11% (29/266) of patients; no Grade 4 hypoxemia was reported. The most commonly reported Grade 3 or 4 adverse event in Control patients was disease progression, reported in 8% (20/263) of patients.

Serious adverse event reports were submitted for 39% (204/529) of patients overall (42% [110/263] in the Control arm and 35% [94/266] in the RSR13 arm). Of these reports, events in 23% (22/266) of RSR13 treated patients were determined by the investigator to be study drug related.

Death was the reason for early termination from the study in 59 patients (32 in the Control arm and 27 in the RSR13 arm). Three deaths were attributed a possible causal link to RSR13 by the investigator (cause of death reported as pneumonia in 1 patient with NSCLC primary, disease progression in 1 patient with breast primary, and acute renal failure in 1 patient with other primary, in this case malignant melanoma).

5.5 Overall Incidence of Adverse Events

The most commonly reported adverse events (>40%) in the RSR13 arm were alopecia, fatigue, headache, nausea, and transient hypoxemia (Table 5.3). The most commonly reported adverse events (>40%) in the Control arm were alopecia and fatigue.

Table 5.3
Adverse Events Occurring in >10% of Patients in Either Treatment arm Regardless of Causality, Study RT-009

Adverse Event	Control (N = 263) %	RSR13 (N = 266) %
Alopecia	49	51
Fatigue	43	49
Headache	33	47
Nausea	30	47
Hypoxemia	4	41
Vomiting	17	38
Radiation dermatitis	25	26
Disease progression	26	17
Constipation	16	22
Dizziness	15	22
Perioral symptoms (during infusion)	N/A	21
Moniliasis	20	16
Anorexia	17	16
Insomnia	18	14
Muscle weakness	15	14
Peripheral edema	11	14
Cough	11	13
Dyspepsia	13	9
Asthenia	14	4
Hypotension	1	14
Anemia	5	12
Dyspnea	14	11
Taste perversion	4	11

5.6 Incidence of RSR13 Treatment-related Adverse Events

Overall, the most commonly reported RSR13-related adverse event was hypoxemia reported in 40% (106/266) of RSR13-treated patients (Table 5.4). The other most common adverse events determined to be RSR13 treatment-related (>30%) were nausea, vomiting, and headache (36% [96/266], 31% [82/266], and 33% [88/266], respectively).

Table 5.4
RSR13-related Adverse Events Occurring in >10% of Patients in Study RT-009

Adverse Event	RSR13 (N = 266) %
Hypoxemia	40
Nausea	36
Headache	33
Vomiting	31
Fatigue	21
Perioral symptoms (during infusion)	20
Dizziness	14
Hypotension	11

5.7 Incidence of Grade 3 and 4 Adverse Events

The majority of treatment-emergent adverse events were Grade 1 (mild) to Grade 2 (moderate) in severity in both treatment arms.

Hypoxemia was reported as a Grade 3 (severe) adverse event in 11% (29/266) of patients in the RSR13 arm and 2% (5/263) of patients in the Control arm (Table 5.5). The other most commonly reported Grade 3 adverse events (>5% in either treatment arm) were headache, reported in 7% of RSR13-treated patients, and disease progression and dyspnea, reported in 7% and 6% of Control patients, respectively. Grade 3 adverse events occurring in 5% of patients in either treatment arm included nausea and vomiting in the RSR13 arm and muscle weakness in the Control arm.

Table 5.5
Grade 3 Adverse Events Occurring in ³3% of Patients in Either Treatment arm Regardless of Causality, Study RT-009

Adverse Event	Control (N = 263) %	RSR13 (N = 266) %
Hypoxemia	2	11
Disease progression	7	4
Headache	3	7
Nausea	3	5
Vomiting	3	5
Fatigue	3	4
Constipation	4	3
Pneumonia	2	3
Muscle weakness	5	2
Dyspnea	6	2

Overall Grade 4 adverse events (considered by the investigator to be life threatening) were reported at comparable frequencies in the 2 treatment arms: reported in 11% (28/263) of Control patients and in 12% (33/266) of RSR13-treated patients. In both treatment arms, disease progression was the most frequently occurring Grade 4 adverse event: reported in 6% of patients in both arms (15/263 Control patients and 16/266 RSR13-treated patients) (Table 5.6). All other Grade 4 adverse events occurred in 1 or 2 patients in both treatment arms with the exception of Grade 4 headache and Grade 4 fatigue (both reported in 3 patients in the Control arm) and Grade 4 acute renal failure (reported in 3 patients in the RSR13 arm).

Table 5.6
Grade 4 Adverse Events Occurring in >1 Patient in Either Treatment arm Regardless of Causality, Study RT-009

Adverse Event	Control (N = 263) %	RSR13 (N = 266) %
Disease progression	13	11
Dyspnea	2	2
Pulmonary embolism	1	2
Acute renal failure	0.4	2
Headache	1	1
Convulsions	1	1
Pneumonia	0	2
Pain	0.4	1
Respiratory insufficiency	0.4	1
Condition aggravated	1	0.4
Coma	1	0.4
Fatigue	1	0
Intracranial hemorrhage	1	0
Pericardial effusion	1	0
Vomiting	0	1
Medication error	0	1
Hypotension	0	1
Hyperglycemia	1	0
Hypokalemia	1	0
Myocardial infarction	1	0

Grade 4 adverse events that were judged related to RSR13 treatment are summarized by tumor type in Table 5.7.

Table 5.7
RSR13 Treatment-related Grade 4 Adverse Events by Site of Primary, Study RT-009

Adverse Event	NSCLC (N = 144) %	Breast (N = 60) %	Other (N = 62) %	All (N = 266) %
Acute renal failure	0	0	5	1
Vomiting	1	0	0	0.4
Stupor	1	0	0	0.4
Pneumonia	1	0	0	0.4
Hypotension	0	0	2	0.4
Tachycardia	0	0	2	0.4
Creatinine blood increased	0	0	2	0.4
Oliguria	0	0	2	0.4
Disease progression	0	2	0	0.4
Deafness	1	0	0	0.4

5.8 Deaths

Based on the patient population being studied and the stage of disease, it was anticipated that the majority of patients would progress and ultimately die of their underlying disease. Through the 1-month follow-up, disease progression was reported as cause of death in 33/263 (13%) patients in the Control arm versus 26/266 (10%) patients in the RSR13 arm (Table 5.8).

The most common cause of death other than disease progression in both treatment arms was pneumonia (Table 5.8) which was reported in 3 patients in the Control arm (all with NSCLC primary) and 5 patients in the RSR13 arm (2 patients with NSCLC primary, 1 patient with primary renal cell carcinoma, 1 patient with primary ovarian cancer, and 1 patient with primary colorectal cancer). An additional patient in the Control arm died as a result of *Pneumocystis carinii* pneumonia (Patient 4062); however, this event was coded by the World Health Organization Adverse Reaction Thesaurus (WHOART) Body System criteria according to the type infection rather than site of infection with this specific organism.

Table 5.8
Summary of Deaths (Number/Percentage of Patients) by Treatment Arm

Cause of Death	Control (N = 263) %	RSR13 (N = 266) %
Disease progression	13	10
Pneumonia	1	2
Respiratory insufficiency	0	1
Edema cerebral	0	0.4
Neurologic deterioration	0.4	0.4
Convulsions	0.4	0
Renal failure acute	0.4	1
Condition aggravated	1	0.4
Cachexia	0.4	0
Anorexia	0.4	0.4
Cardiac arrest	0	0.4
Dehydration	0.4	0.4
Diabetes mellitus aggravated	0.4	0
Somnolence	0.4	0.4
Cerebrovascular disorder	0.4	0.4
Cerebral hemorrhage	0.4	0
Embolism pulmonary	0.4	0
Left ventricular dysfunction	0.4	0
Pneumocystis carinii infection	0.4	0
Sepsis	0.4	0
Stevens Johnson syndrome	0.4	0

Three deaths were attributed as having a “possible” causal link to the study drug by the investigator (Table 5.9).

Table 5.9
Summary of Deaths Considered by the Investigator to Have a Possible, Probable, or Definite Relationship to Study Drug

Patient #	Gender/Age	Primary Site	Allos SAE #	WHOART Preferred Term (Verbatim)
1023	Male/63	NSCLC	0302	Pneumonia (pneumonia)
3040	Female/71	Breast	0301	Disease progression (disease progression)
4084	Male/49	Other[a]	0398	Renal failure acute (acute renal failure)

[a] Malignant melanoma

5.9 Adverse Events Identified as Significant Components of the RSR13 Safety Profile

Eight treatment-emergent adverse events or adverse event categories were identified as components of the RSR13 safety profile. Factors considered in this determination were the incidence of the event, attribution to study treatment, mechanism of action of the investigative product, and evaluation of safety data in study RT-009. Table 5.10 lists the adverse events/categories and the incidence of these events in study RT-009, as well as for all patients who were randomized to the RSR13 arm in all studies.

Table 5.10
Overall Incidence of Treatment-emergent Adverse Events/Adverse Event Categories Identified as Significant or Likely Components of RSR13 Safety Profile Regardless of Causality, Study RT-009

Adverse Event	Control (N = 263) %	RSR13 (N = 266) %	All RSR13 (N = 538) %
Nausea	30	47	52
Vomiting	17	38	38
Headache	33	47	51
Hypoxemia	4	41	37
Dizziness	15	22	25
Hypotension	1	14	13
Infusion symptoms	0	27	30
Rash/allergic reaction	8	12	16
Anemia	5	12	16
Renal dysfunction	1	8	9

5.10 Concomitant Medications

No prospective drug-drug interaction studies have been conducted in humans. Results of in vitro studies have indicated that RSR13 may be a weak metabolic inhibitor of hepatic CYP2C9 and CYP3A4 isoenzymes.

In study RT-009, drug-drug interactions were explored with respect to the distribution of selected treatment-emergent adverse events by body system, preferred term, study, selected concomitant medication, and/or medical history. Patients receiving RSR13 with a positive history of cardiovascular diseases or known concomitant anti-hypertensive treatment had a higher incidence and severity of the following treatment-emergent adverse events: hypoxemia, hypotension, and renal dysfunction. In study RT-009, the management of these events consisted of modifications of the anti-hypertensive regimen (dose reduction, omission of doses, change in schedule) as well as dose modifications of RSR13. With the above modifications, the majority of patients were able to receive RSR13 throughout the planned treatment period.

5.11 Relationship of Adverse Events to Dose, Dose Regimen, and Treatment Duration

RSR13 is dosed on a mg/kg body weight basis. RSR13 binds to hemoglobin and the compartment of drug distribution is represented by the total blood volume of the patient. However, the total blood volume does not increase proportionally with body weight. Within gender, patients with a higher body weight received higher total doses on a mg/kg basis while their total blood volume was more comparable to patients at lower weight. Female patients generally achieved higher concentrations of RSR13 in plasma and RBCs. Female patients with a weight over 70 kg and males with a weight over 95 kg demonstrated a higher incidence of RSR13 treatment-related adverse events leading to the implementation of dosing-adjustment guidelines. The guidelines included these weights as cut-off values for the determination of starting dose and subsequent doses of RSR13. The dosing-adjustment guidelines also took into consideration the patient's adverse event profile when the starting dose or subsequent dosing was determined.

5.12 Summary of RSR13 Safety Profile

1) Safety data from over 500 RSR13-treated oncology patients indicate an acceptable safety profile for RSR13
2) Eight adverse events have been identified as components of the RSR13 safety profile
3) There was a consistent incidence of the adverse events identified as components of the RSR13 safety profile between the RSR13 arm in study RT-009 and safety data from 535 oncology patients who received at least 1 dose of RSR13

6.0 CONCLUSIONS

RSR13 is the first of a new class of agents, allosteric modifiers of hemoglobin. The goal of the initial clinical study of RSR13 (HV-001) was to administer a dose of RSR13 sufficient to induce the desired PD endpoint, increasing whole blood p50 by 10 mmHg. Following HV-001, the first study of RSR13 in patients with cancer receiving RT (RT-002) was conducted. RT-002 confirmed the feasibility of administering doses of RSR13 sufficient to reach the desired PD endpoint and, together with the previous study (HV-001) and subsequent studies (RT-008 and RT-010), confirmed the strong correlation between RSR13 concentration in the RBC and p50 shift. Based on these studies, a dose of RSR13 of 75-100 mg/kg/day was identified as optimal for further testing, and was the dose selected for patients with brain metastases enrolled in the pivotal Phase 3 study (Study RT-009). Study RT-009 was the culmination of 10 years of clinical development of RSR13 as a radiation sensitizer. As such, it represents the first successful randomized study of a non-cytotoxic radiation sensitizer in patients with any solid tumor.

The prognosis of patients with brain metastases has not changed for the past 2 decades. The administration of WBRT has been shown to increase survival and to delay neurologic progression, but since its introduction, no meaningful improvement in the outcome of these patients has been realized. While some selected patients benefit from resection or stereotactic radiosurgery (SRS), the majority of patients with brain metastases are not candidates for either of these interventions. Furthermore, the use of SRS does not eliminate the need for WBRT, as randomized studies have shown that the addition of WBRT to SRS is superior to SRS alone. Lack of progress for these patients is evidenced by the results of the Control Arm of study RT-009 which showed an MST of 4.6 months, almost identical compared to the MST of patients in the RTOG BMD treated over the last 25 years.

The results of study RT-009 demonstrate that RSR13 as an adjunct to WBRT can improve the outcome of patients with brain metastases without adversely affecting their QOL. Despite the fact that the primary analysis for survival in the two co-primary populations of study RT-009 revealed a difference in survival that did not reach statistical significance by unadjusted log-rank, several pieces of evidence confirm the activity of RSR13 in this setting:

1. The analysis of survival in the NSCLC/Breast cancer co-primary population revealed a 38% improvement in MST due to RSR13 (MST: Control 4.4 months versus RSR13 Arm 6.0 months) with a strong trend towards statistical significance ($p = 0.07$, unadjusted log-rank). The primary analysis of survival for study RT-009 took place after a prespecified number of events had occurred and with a minimum follow-up of 6 months. When these results are analyzed with an additional follow-up of 12 months, the comparison between the arms in the NSCLC/Breast co-primary population reaches significance ($p=0.05$).
2. Imbalances in the relative frequency of prognostic factors favoring the Control arm require the use of a Cox multiple regression model to accurately assess the treatment effect in study RT-009. There is ample support in the literature for the use of a Cox model in this setting, and in fact, the protocol and the SAP specified that a Cox multiple regression analysis would be conducted as part of the statistical analysis of this study. All covariates included in the model were prespecified, the Cox model was run for each of 48 possible combinations of

covariates, and the RSR13 indicator variable was statistically significant in 48/48 of the models (mean HR = 0.76). We therefore conclude that when adjusted for imbalances in prognostic variables using a Cox model, the results of study RT-009 demonstrated a statistically significant difference in survival in favor of the patients that received RSR13 over the Control arm.

3. While the results of study RT-009 as a whole showed evidence of activity for RSR13 across tumor types, these results were in large part driven by the treatment effect observed in patients with brain metastases originating from breast cancer. Thus, we analyzed the results in this population separately. The results of the study in this population reveal:
   a. Clinically meaningful improvement in survival (4.6 months compared to 8.7 months).
   b. The reduction in the risk of death produced by RSR13 in breast cancer patients was highly consistent whether analyzed by unadjusted log-rank (HR = 0.55) or by Cox multiple regression (HR = 0.51).
   c. Significant improvement in response rate by unadjusted log-rank.
   d. Stable or improved QOL measurements.
   e. Consistent Treatment Effect: When primary breast cancer patients were analyzed according to 16 prespecified covariates, the RSR13 treatment-effect was consistent across all covariate subgroups.
4. While the results in patients with NSCLC were not what we expected, analyses of the dosing, and adjustment of the results for adequate dosing and favorable ("successful") pharmacokinetics, strongly suggest that if dosed adequately, these patients should derive benefit from the addition of RSR13 to WBRT.
5. RSR13 is aimed at increasing survival by improving local control. The clearest evidence supporting the principle that RSR13 improves the effectiveness of WBRT comes from the statistically significant improvement in response rate observed in the co-primary population of patients with NSCLC/breast cancer. A trend towards significance was also seen in the co-primary population of all randomized patients. It is important to point out that response was associated with longer survival, both in studies RT-008 and in RT-009, in the latter, independently of study arm.

The results of study RT-009 confirmed what previous studies with RSR13 had suggested: RSR13 is safe when administered to cancer patients as an adjunct to RT. This is supported by the low frequency of Grade 3-4 adverse events in study RT-009.

The most characteristic adverse event observed with RSR13 is transient hypoxemia. This is a direct result of the PD effect of the drug and it is associated with its activity as a radiation sensitizer. It is important to stress the fact that 73% of all patients in study RT-009 who experienced hypoxemia as an adverse event were asymptomatic and the only treatment required was supplemental oxygen.

In conclusion, RSR13 represents not only the first non-cytotoxic radiation sensitizer to demonstrate a survival benefit, but also the first clinically meaningful advance since the introduction of WBRT for patients with brain metastases originating from breast cancer and who are candidates for WBRT.

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